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Review

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Novel treatment approaches utilizing antibody-drug conjugates in breast cancer

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Antibody-drug conjugates (ADCs) are rapidly changing the way we treat patients with breast cancer. Despite this progress, many unanswered questions remain regarding the sequencing of different ADCs with similar payloads, optimal combinations, drug design strategies to limit off-target toxicities, biomarkers to define antigen positivity, and the use of ADCs in the neoadjuvant and adjuvant settings. In this review, we summarize novel ADC approaches in breast cancer treatment, including potential improvements in ADC payloads, linkers, targets, and drug delivery. We also evaluate novel strategies to combine ADCs with other agents, such as targeted drugs and immune checkpoint inhibitors. To improve patient selection, the development of quantitative biomarkers is reviewed, including HER2 mRNA, immunofluorescence-based assays, mass spectrometry, liquid biopsies, digital pathology, and molecular imaging-based approaches. Lastly, we evaluate the potential to incorporate ADCs into the early-stage setting, including evaluating currently published and ongoing clinical trials. This review highlights the potential for ADCs to shift the treatment paradigm in both the advanced and early-stage settings. We further demonstrate the complexity and challenges of improving ADCs to enhance targeting of tumor vulnerabilities while limiting toxicity through rationale drug development strategies to enhance the therapeutic window, linker technology, and payload variability to continue to improve outcomes for patients with breast cancer.

The first HER2-targeting antibody-drug conjugate (ADC), trastuzumab emtansine, which consists of a HER2 antibody, non-cleavable linker, and maytansine payload, was approved by the Food and Drug Administration (FDA) in 2013 for patients with HER2-positive metastatic breast cancer with a subsequent approval in the adjuvant setting in 2019 for patients with residual disease after neoadjuvant chemotherapy combined with HER2-directed therapy[1,2]. Since that time, the field of ADCs has evolved rapidly across oncology. As of February 2025, more than ten ADCs have been approved by the FDA across all tumor types, including three additional ADCs for patients with advanced breast cancer: trastuzumab deruxtecan (targeting HER2), sacituzumab govitecan (targeting trophoblast cell surface antigen 2 (TROP2)), and datopotamab deruxtecan (targeting TROP2), all of which contain topoisomerase I payloads (Table 1)[3–12]. Compared to standard-of-care chemotherapy, trastuzumab deruxtecan and sacituzumab govitecan have demonstrated significant improvement in progression-free survival (PFS), overall survival (OS), and quality of life in Phase III clinical trials, while datopotamab deruxtecan has improved PFS[4–13]. Trastuzumab deruxtecan is currently approved for patients with HER2 overexpression, HER2-low, and HER2-ultralow advanced breast cancer. Sacituzumab govitecan is approved for patients with advanced hormone receptor-positive (HR +) HER2- and triple-negative breast cancers (TNBC) with approval independent of TROP2 expression, and datopotamab deruxtecan is approved for patients with HR + HER2- advanced breast cancer. However, clinical trials comparing the efficacy of trastuzumab deruxtecan, sacituzumab govitecan, and datopotamab deruxtecan do not currently exist, and real-world analyses have demonstrated lower than anticipated benefit of using these drugs in sequence, likely due to similar cytotoxic payloads with topoisomerase I inhibitors[14,15]. While there has been considerable progress in the field of ADC drug development, there remain significant unmet needs and unanswered questions regarding optimal ADC design, combination strategies, sequencing of different ADCs, and biomarker development in both the metastatic and early-stage settings. Here, we review novel approaches to the design and implementation of ADCs across the spectrum of breast cancer treatment, along with biomarker investigations essential to enhancing drug development strategies.

ADC sequencing

One of the biggest gaps in the current literature is determining how best to administer ADCs in sequence based on target expression, payload, and mechanisms of resistance. Based on DESTINY-Breast02, we have clear

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Table 1 | FDA-approved ADCs in breast cancer

	Trastuzumab emtansine	Trastuzumab deruxtecan	Sacituzumab govitecan	Datopotomab deruxtecan
FDA approval(s)	2013, 2019	2019, 2022, 2025	2021, 2023	2025
Indication(s)	HER2 overexpressed	HER2 overexpressed, HER2-low, HER2-ultralow	TNBC, HR + HER2 negative	HR + HER2 negative
Metastatic	Yes	Yes	Yes	Yes
Early stage	Yes	No	No	No
Target	HER2	HER2	TROP2	TROP2
Drug-to-antibody ratio	3.5	8	7.6	4
Cleavable linker	No	Yes	Yes	No
Payload	Maytansine	Topoisomerase I	Topoisomerase I	Topoisomerase I

evidence that utilizing ADCs targeting HER2 in sequence with different payloads (e.g., trastuzumab deruxtecan after trastuzumab emtansine) is an effective therapeutic approach to overcome resistance to the prior ADC[4]. However, sequential use of HER2-targeting trastuzumab deruxtecan and TROP2-targeting sacituzumab govitecan in a real-world analysis of 179 patients with HER2-low metastatic breast cancer, with or without intervening chemotherapy, has yielded a median PFS for the second ADC of only 2.7 months (95% CI: 2.4–3.3). Nonetheless, 13 patients benefited from the second ADC for more than 6 months, indicating cross-resistance is not present for all patients[15]. Other retrospective data were similar, demonstrating a median PFS for the second ADC of less than three months with the same antibody target[14]. Biomarkers for ADC selection and sequencing are lacking for clinical use. The objective of the TRADE DXd study (NCT06533826) is to determine whether utilizing trastuzumab deruxtecan before or after datopotomab deruxtecan will impact therapeutic efficacy in HER2-low metastatic breast cancer. A robust biomarker analysis is planned to address the optimal sequencing strategy of these two ADCs that target different receptors (HER2 and TROP2) and have the same payload (deruxtecan). In HER2+ advanced breast cancer, studies are evaluating a HER2-targeting ADC with a different payload such as ARX788 (HER2-targeting monoclonal antibody conjugated to a cytotoxic tubulin inhibitor, ACE-BREAST-03, NCT04829604) or an ADC with a different target such as sacituzumab govitecan in combination with trastuzumab (SATEEN, NCT06100874), in patients who have previously received trastuzumab deruxtecan. Additional studies are necessary to characterize the optimal selection of ADCs targeting the same receptor or different receptors, define ADCs with non-overlapping toxicities, and understand mechanisms of resistance to improve the sequencing of ADCs.

Novel approaches: ADC payloads, linkers, targets, and drug delivery

Given data from real-world studies demonstrating decreased efficacy when ADCs with similar cytotoxic payloads are used in sequence, efforts are ongoing to develop ADCs with novel targets, payloads, and designs with the goal to maximize the therapeutic index that is different than non-conjugated (free payload) chemotherapeutics.

Novel TROP2 ADCs

Datopotomab deruxtecan targets TROP2 and has a cleavable tetrapeptide linker with a topoisomerase 1 payload (drug-to-antibody ratio (DAR) of 4), similar to trastuzumab deruxtecan. In preclinical studies, datopotomab deruxtecan demonstrated therapeutic efficacy in TROP2-high tumor models but not in tumors with low TROP2[16]. An objective-response rate (ORR) of 26.8% was observed for patients with advanced HR + HER2- breast cancer and 31.8% for patients with TNBC[17]. The TROPION-Breast01 trial (NCT05104866) compared datopotomab deruxtecan versus single-agent chemotherapy in patients with advanced HR + HER2-negative breast cancer with up to two lines of prior chemotherapy and demonstrated improvement in PFS but not OS, with the most common toxicities including nausea, stomatitis, and neutropenia[18,19]. Based on this trial, in January 2025, datopotamab deruxtecan was approved by the FDA for patients with advanced HR + HER2- breast cancer who have received both prior endocrine therapy and chemotherapy. TROPION-Breast05 (NCT06103864) is a phase III study assessing datopotamab deruxtecan with or without durvalumab versus chemotherapy and pembrolizumab in patients with metastatic PD-L1-positive TNBC based on the 22C3 assay combined positive score of 10 or higher, while TROPION-Breast02 (NCT05374512) is evaluating datopotamab deruxtecan in patients with PD-L1 negativity[20,21]. Similar studies are underway with sacituzumab govitecan in patients who are PD-L1 positive (ASCENT-04/NCT05382286) and PD-L1 negative (ASCENT-03/NCT05382299). If positive, these studies would move ADC therapy to the first-line setting for patients with metastatic TNBC and warrant a better understanding of sequencing and selection of ADCs for later lines of treatment.

Sacituzumab tirumotecan is a TROP2 ADC conjugated to a belotecan-derivative topoisomerase I payload via a hydrolytically linker (DAR 7.4). This hydrolytically linker leads to extracellular pH-sensitive cleavage and intracellular enzymatic cleavage, followed by the release of the membrane-permeable payload, which enables the bystander effect. Sacituzumab tirumotecan has demonstrated a PFS improvement of 3.4 months as compared to standard chemotherapy in the phase III OptiTROP-Breast01 trial, and this ADC is now approved in China for patients with TNBC after two prior lines of therapy[22]. Multiple other TROP2 ADCs are in preclinical development, and with more than 10 TROP2 ADCs in clinical development, further improvements in efficacy and decreased toxicity are anticipated[23].

Novel payloads

Studies are underway to develop and evaluate different cytotoxic payloads, beyond topoisomerase I, to expand the delivery of novel payloads while still targeting the HER2 protein. Beyond topoisomerase I inhibition, the vast majority of ADCs in clinical development include payloads related to microtubule inhibition and DNA alkylation, highlighting the importance of expanding the armamentarium to deliver novel payloads to permit future ADC combination and sequencing strategies[3]. Trastuzumab duocarmazine targets HER2 with a cleavable linker and a pro-drug duocarmycin payload (DAR 2.8)[24]. After HER2 binding and internalization, the linker is cleaved in the lysosome by proteases, and the active toxin is released, which alkylates DNA in the minor groove, resulting in DNA damage and cell death. The cleavage of the payload from the linker can also occur intracellularly, leading to a bystander effect not mediated by HER2 binding. This drug was evaluated in the phase III TULIP trial in patients with HER2-overexpressed advanced breast cancer after progression on at least two lines of therapy in the metastatic setting or trastuzumab emtansine[25]. Compared to chemotherapy, there was a 2.1-month improvement in PFS and a non-significant improvement of 3.7 months in OS. Ocular toxicity was common with trastuzumab duocarmazine, including all-grade toxicity of greater than 30% reported for keratitis, conjunctivitis, and dry eye, and grade 3 or higher toxicity of 12.2%, 5.6%, and 4.2%, respectively. However, the European Medicines Agency's human medicine committee had concerns about the interpretation of the trial data, ultimately leading to a withdrawal of the application in September 2023.

ARX788 (anvatabart opadotin) is site-specifically conjugated to a tubulin inhibitor payload, AS269, via a non-cleavable linker. Upon binding and internalization, tubulin polymerization is inhibited, resulting in G2/M phase arrest and tumor cell apoptosis. ARX788 has demonstrated therapeutic activity in preclinical models with HER2 overexpression that were resistant to trastuzumab emtansine[26,27]. At the recommended phase 2 dose, the ORR was 65.5% with a median PFS of 17 months[28]. However, in the phase I study, approximately 35% of patients experienced ILD/pneumonitis, although the vast majority were low grade, with only two patients having grade 3 or higher ILD/pneumonitis. The randomized phase 3 ACE-Breast-02 study that was performed in China reported an improvement in PFS compared to lapatinib and capecitabine in patients with HER2-positive advanced breast cancer[29]. This study reported high rates of ILD/pneumonitis (32.7% all grade and 5.9% grade 3 or higher, and also high rates of all-grade ocular and hepatotoxicity (>70%)[30]. These toxicities may limit combination strategies with other ADCs that cause similar toxicity profiles.

Disitamab vedotin (RC48) is comprised of the HER2-targeting hertuzumab coupling monomethylauristatin E (MMAE) (DAR 4) via a cleavable linker with ORRs observed across HER2-overexpressed and HER2-low advanced breast cancer[31]. Multiple other ADCs and payloads are being explored, including ADCs containing monomethylauristatin F (FS-1502)[32], MMAE (A166)[33], auristatin (PF-06804103)[34], pyrrolobenzodiazpine (DHES0815A)[35], and eribulin payloads (BB-1701)[36]. These drugs are in various stages of development and are summarized in Supplemental Table 1.

Improving linker technology

Strategies to improve conjugation of the linker and topoisomerase I payload to limit early release into the bloodstream are underway with the goal of decreasing systemic toxicity[37]. As an example, SHR-A1811 (trastuzumab rezetecan) is an ADC targeting HER2 (DAR 5.7) with a chiral cyclopropyl group that was engineered between the linker and toxin. The goal of this chemistry is to increase the stability of the toxin in the bloodstream to prevent unintended release that may be responsible for off-target drug toxicity, while also optimizing membrane permeability. In this study, ILD was reported in 2.6% of patients across multiple solid tumors. Phase III studies are ongoing and will be important to determine whether lower rates of ILD/pneumonitis are observed with SHR-A1811 compared to rates observed with trastuzumab deruxtecan, which occurs in approximately 12% of patients[38].

ESG401 is a TROP2 ADC (DAR 8), developed with a proprietary stable linker to potentially decrease toxicity with an SN38 payload[23]. The release of the SN38 payload occurs after ESG401 internalization in a TROP2 expression-dependent manner. In contrast to sacituzumab govitecan, which has an unstable linker design that may contribute to the development of off-target toxicity, including diarrhea and neutropenia, the stable linker of ESG401 was evaluated in a 40-patient single-arm study. While there were some differences in the ADC design, similar types of toxicity to sacituzumab govitecan were observed, including cytopenias, nausea, vomiting, fatigue, and diarrhea, although with a signal of drug efficacy based on an ORR of 34.2% and a disease control rate of 65.8%. This drug highlights that while efforts to improve the linker technology are critical, reduced toxicity was not clearly achieved with this drug. These studies highlight the current limitations in our understanding of how linker stability (or instability) in the circulation may affect premature payload release to non-target tissues, and further preclinical development is needed to understand this highly complex process. We anticipate that improvements in linker technology will lead to decreased off-target toxicity in the future.

Novel drug targets

Patritumab deruxtecan is a HER3-targeting ADC with an exatecan-derived topoisomerase I inhibitor payload and a tetrapeptide cleavable linker (DAR 4). In a phase I/II clinical trial of patients with HR + HER2- metastatic breast cancer, patritumab deruxtecan had an ORR of 30.1% and OS of 7.4 months with responses independent of HER3 IHC and *ERBB3* mRNA expression[39]. Further studies are evaluating patritumab deruxtecan after progression on a CDK4/6 inhibitor and one line of chemotherapy and across heavily pre-treated patients with metastatic disease[40,41]. AMT-562 was developed as a novel compound aimed at targeting lower levels of HER3 expression in cells[42]. This drug was developed as an anti-HER3 antibody with a cleavable linker and a hydrophilic self-immolative T moiety conjugated to exatecan. The goal of this design is to increase stability in the bloodstream while also enhancing potency with exatecan, which is the precursor to DXd, with improved cell permeability that may lead to enhanced bystander effect. Preclinical studies demonstrated evidence of clinical activity in organoid models and patient-derived xenografts with low levels of HER3 expression. Further, in these models, AMT-562 demonstrated potential synergy to combine with other drugs.

Multiple studies are evaluating the CD276/B7-H3 target, which is overexpressed across a variety of different tumor types in both cancer cells and tumor-associated stroma, with approximately 75% of breast cancers expressing the target[43]. Preclinical studies are evaluating ADCs targeting B7-H3 with a talirine-type pyrrolobenzodiazepine payload in TNBC xenograft models[44]. This approach utilized human antibodies with affinity towards mouse and human antigens and site-specific maleimide-mediated drug conjugation. Whether this drug will be safe and effective in patients is not yet known. Additional studies have explored an ADC with dual-payload targeting B7-H3 to deliver both a cytotoxic payload and an immunoregulating Toll-like receptor 7/8 agonist[45]. The goal of this agent, which has only been evaluated in preclinical studies to date, is to combine the cytotoxicity and immune-stimulatory properties of the drug. Another example of an anti-HER2 ADC with dual payload that has shown efficacy in preclinical models of breast cancer is trastuzumab containing both MMAE and monomethyl auristatin F[46]. Similarly, B7H4 is being explored as an investigational target with various targets including an MMAE payload and AZD8025 (puxitatug samrotecan) with a topoisomerase I inhibitor payload (NCT05123482) in breast cancer and other tumor types[47,48]. While EGFR antibodies have shown limited promise in advanced breast cancer, ADCs are in development to target and deliver cell cycle inhibitors, such as SNS-032, in a targeted manner in TNBC xenograft models[49].

A variety of drugs with different targets are currently being evaluated in early-phase clinical trials across multiple tumor types, including patients with advanced breast cancer, such as LIV1, mesothelin, Nectin-4, and tissue factor[50,51]. In addition, bispecific antibody-drug conjugates, such as a drug targeting both HER2 and HER3, are in development with promising preclinical activity[52]. Bispecific antibodies targeting different sites on the same antigen have also shown to improve the internalization and efficacy of the ADC, and this novel class of drugs holds particular promise to target more than one epitope (either two of the same target such as HER2 or two separate proteins) to selectively target the tumor with specific antigens, improve internalization, and potentially limit off-target toxicity[53,54].

Drug delivery techniques

In terms of novel drug delivery techniques, sacituzumab govitecan has been explored in a phase 0 trial evaluating direct administration of the ADC to the brain during craniotomy[55]. Based on local drug delivery in this study, the PFS was 8 months, and lower rates of drug toxicity were observed compared to what is reported with systemic administration of sacituzumab govitecan. In an exploratory analysis, the ORR was 38% for the treatment of metastatic disease in the brain. Further studies are needed to evaluate delivery techniques directed toward both local and metastatic sites to enhance the uptake of ADCs in a targeted manner and to limit systemic toxicity.

Novel drug combinations

Careful consideration of optimal combination therapy and dosing are needed. For example, initial studies with trastuzumab emtansine in combination with docetaxel with or without pertuzumab resulted in nearly half of the patients requiring dose reductions[56]. In contrast, prior studies have demonstrated the safety and tolerability of combining ADCs with endocrine

therapy, highlighting the capability of combining ADCs with drugs that have non-overlapping toxicity profiles[57].

Combination strategies aimed to enhance the anti-tumor effect of ADC therapeutics are being tested in early-phase clinical trials (Table 2). There has been significant interest in combining DNA damage repair pathways inhibitors with ADCs containing a topoisomerase I payload[58]. As proof of principle, a clinical trial explored the combination of sacituzumab govitecan with talazoparib, a Poly(ADP-ribose) polymerase (PARP) inhibitor, due to proposed synergy with topoisomerase I inhibition[59]. The trial demonstrated that concurrent dosing of these drugs was highly myelosuppressive, leading to treatment delays and discontinuation, while, in contrast, sequential dosing of these drugs could minimize overlapping toxicities while enhancing therapeutic efficacy.

The potential of ADCs to elicit antibody-dependent cell-mediated cytotoxicity renders the investigation of their combination with immune checkpoint inhibitors an attractive strategy. BEGONIA is a multi-arm platform study evaluating durvalumab and various ADCs as first-line treatment for patients with TNBC, with preliminary safety and efficacy data reported for patients treated with durvalumab and trastuzumab deruxtecan and durvalumab combined with datopotomab deruxtecan[60,61]. Early data are promising, with confirmed ORRs ranging from approximately 57%–79% with responses observed irrespective of PD-L1 expression and a small subset of patients achieving a complete response. The combination appears to have manageable toxicity profiles, although, as a single-arm study, the degree of benefit of the combination versus the ADC alone is currently unknown, and the degree of benefit will be better defined in phase III randomized studies in the future.

Both preclinically and clinically, drug combinations are being explored to pharmacologically modulate or enhance target expression. For example, in a preclinical model, decitabine enhanced TROP2 expression in a metaplastic breast cancer model to potentiate the effect of sacituzumab govitecan[62]. While sacituzumab govitecan is currently FDA approved independent of TROP2 expression, methods to enhance target engagement may prove efficacious. The combination of trastuzumab deruxtecan and neratinib, an irreversible tyrosine kinase inhibitor, is being evaluated in an ongoing phase I study of patients with HER2 overexpression, amplification, or *HER2* activating mutations, based on preclinical work demonstrating enhanced endocytosis via HSP90 binding to the HER2 receptor, leading to enhanced uptake of trastuzumab deruxtecan via ubiquitination and internalization[63,64]. Importantly, in this study, paired tissue biopsies will be obtained before and after initiation of neratinib to validate the hypothesis of enhanced delivery of the DXd payload in patients. Other work has demonstrated the potential of statins to enhance HER2 availability and trastuzumab efficacy in preclinical models of HER2-expressing breast tumors[65]. Combination strategies with trastuzumab deruxtecan are also being explored preclinically, such as adavosertib, a Wee1 kinase inhibitor, across a variety of tumor types with signals of activity in those with Cyclin E amplifications[66].

To date, combining ADCs has been challenging, likely due to significant overlap of payload toxicity, further emphasizing the need to expand ADC design and dosing strategies. Novel payloads will also enhance our ability to sequence ADCs[67]. A clinical trial utilizing ADCs in sequence, such as the SAPPHO study (NCT06439693), is exploring sequential lines of therapy, including ADCs, for curative-intent treatment for patients with de novo HER2+ metastatic breast cancer. In addition, a Phase Ib/II study evaluating both concurrent and alternating dosing schedules of patritumab deruxtecan and trastuzumab deruxtecan is planned for patients with advanced HER2-low breast cancer (HERTHENA-Breast02). As proof of principle, in a study of patients with metastatic urothelial carcinoma, two ADCs could be combined based on the drugs having non-overlapping toxicity profiles, given that the study utilized ADCs with both different targets and different payloads[68]. In summary, combination strategies must consider the expression of the drug target, better characterization of the precise mechanism of action of each ADC, potential overlapping drug toxicities, and investigation of unique dosing regimens to enhance the development of rationale and safe combinatorial strategies.

Biomarkers for ADC selection and response

We are only beginning to understand how to utilize biomarkers to optimally select patients for ADC therapy. With the development of multiple ADCs with similar designs and payloads, it will be critical to identify subsets of patients who will benefit from an individual drug or combination strategy through improved characterization of target expression and tumor heterogeneity[69].

HER2

While initially promising as a predictive biomarker for response to trastuzumab deruxtecan, the utility of HER2 expression by IHC has decreased over time, as patients with HER2 low and HER2 ultralow advanced breast cancer appear to have similar PFS in the DESTINY-Breast06 trial. Furthermore, the data regarding HER2 ultralow contributes to our interpretation of the DAISY trial, which reported an ORR of approximately 30% in patients who were HER2 IHC 0, but HER2 ultralow status was not evaluated at the time[70]. For clinical use, it is unclear whether the site of disease (e.g., primary versus metastatic) biopsies are important to define HER2 expression for clinical response, reinforcing that HER2-low appears to be a drug-defined category, rather than a biological breast cancer subtype[71,72]. Furthermore, there is considerable heterogeneity of HER2 expression, as evidenced by post-mortem biopsies evaluating multiple metastatic samples within the same patient, demonstrating intra-patient and intra-organ heterogeneity[73]. There is uncertainty regarding the long-term utility of HER2 IHC as a predictive biomarker given the heterogeneity of expression and lack of concordance among pathologists, particularly to define low levels of HER2 expression[74]. Therefore, novel quantitative assays are in development, including exploring the use of HER2 mRNA[75], immunofluorescence-based assays[76], mass spectrometry[77], and digital pathology approaches[78], some of which incorporate machine learning and artificial intelligence (AI) technologies.

High levels of HER2 gene expression were associated with longer PFS with trastuzumab deruxtecan, based on a correlative analysis from DESTINY-Breast04[79]. The HER2DX assay (Reveal Genomics) is also a promising assay in both the advanced and early-stage settings across a variety of ADCs, including trastuzumab emtansine, to differentiate response based on levels of ERBB2 expression[75,80]. In addition, quantitative immunofluorescence has been utilized to quantify HER2 protein expression, which was associated with time to next treatment in a sample of 51 patients treated with trastuzumab deruxtecan[76]. Multiple-reaction mass spectrometry is another approach developed to measure HER2 protein expression more quantitatively as compared to IHC and may be a useful tool in the future, particularly to differentiate among HER2 0, ultralow, and low[77,81]. Image-analysis approaches demonstrate the potential to assess digitized images of slides quantitatively to evaluate the spatial distribution of HER2 expression and nearby cells to characterize and better differentiate clinical response compared to HER2 IHC[82]. AI approaches may also aid pathologists in distinguishing HER2 0 and HER2 1+ cases, and AI can also improve the accuracy of defining tumor heterogeneity[78,83]. Further work in this space will help clarify the clinical utility of these biomarkers to define response and selection of HER2-directed ADCs.

Molecular imaging-based approaches

PET imaging with anti-HER2 radiolabeled antibodies is an imaging approach that enables the visualization of HER2 throughout the body. Trastuzumab radiolabeled with the positron emitters zirconium-89 ([^{89}Zr]trastuzumab) and copper-64 ([^{64}Cu]DOTA-trastuzumab) are the most widely used PET radiopharmaceuticals for HER2 detection. [^{89}Zr]trastuzumab and [^{64}Cu]DOTA-trastuzumab detect HER2 in preclinical models of varying HER2 protein levels[84]. Dehdashti et al. have demonstrated the potential of ^{89}Zr-trastuzumab PET/CT to differentiate between HER2-positive and HER2-negative breast tumors[85]. The uptake of ^{89}Zr-

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Table 2 | Representative ongoing clinical trials of ADC combination therapies in breast cancer

Name of Trial	NCT #	Phase	Status	ADC	ADC target antigen	ADC payload	DAR	Combination therapeutic	MOA	Study arms	Indication	Primary endpoint
AZD8205 Given Alone or in Combination with Anti-cancer Drugs, in Participants with Advanced or Metastatic Solid Malignancies (BLUESTAR)	NCT05123482	I/IIa	Recruiting	Puxitatug samrotecan (AZD8205)	B7-H4	Topoisomerase I inhibitor	8	Rilvegostomig	TIGIT and PD-1 inhibitor	Arm A: AZD8205 monotherapy Arm B: AZD8205 + rilvegostomig	Locally advanced/ recurrent or metastatic breast, ovarian, BTC, or endometrial cancer	AEs and SAEs DLTs
Dato-DXd With or Without Durvalumab Compared with ICC in Combination with Pembrolizumab in Patients With PD-L1 Positive Locally Recurrent Inoperable or Metastatic TNBC (TROPION-Breast05)	NCT06103864	III	Recruiting	Datopotamab deruxtecan	TROP2	Topoisomerase I inhibitor	4	Durvalumab	PD-L1 inhibitor	Arm A: Dato-DXd + durvalumab Arm B: ICC (paclitaxel, nab-paclitaxel or gemcitabine + carboplatin) + pembrolizumab Arm C: Dato-DXd monotherapy	PD-L1 positive TNBC, locally recurrent, or metastatic	PFS
Disitamab Vedotin Alone or With Other Anti-cancer Drugs in Solid Tumors	NCT06157892	Ib/II	Recruiting	Disitamab vedotin (RC48)	HER2	MMAE	4	Tucatinib	TKI	Cohort A: HER2-low 2 L or 3 L breast cancer Arm A: RC48 monotherapy Arm B: RC48 + tucatinib Cohort B: HER2 + 3 L or higher breast cancer Arm A: RC48 monotherapy Arm B: RC48 + tucatinib	HER2+ and low-expressing breast cancer& HER2 low-expressing gastric or GE junction, locally advanced, unresectable, or metastatic	AEs DLTs ORR
Disitamab Vedotin and Anlotinib in Patients With HR-Negative, HER2-Low-Expressing Metastatic Breast Cancer	NCT06000033	II	Not Yet Recruiting	Disitamab vedotin (RC48)	HER2	MMAE	4	Anlotinib	TKI	RC48 + anlotinib	HR-negative, HER2 low-expressing locally advanced or metastatic breast cancer	ORR
GQ1001 Combined with Pyrotinib for Treatment with HER2+ Metastatic Breast Cancer (GRACE)	NCT05575804	Ib/II	Recruiting	GQ1001	HER2	DM1	1.8	Pyrotinib	TKI	Arm A: GQ1001 + pyrotinib Arm B: Pyrotinib + capecitabine	HER2+ locally advanced or metastatic breast cancer	AEs DLTs MTD ORR
TROP2 ADC LCB84 Single Agent and in Combination with an Anti-PD-1 Ab in Advanced Solid Tumors	NCT05941507	I/II	Recruiting	LCB84	TROP2	MMAE	4	Anti-PD-1 Ab	PD-1 inhibitor	Arm A: LCB84 monotherapy Arm B: LCB84 + anti-PD-1	Advanced breast cancer and other solid tumors	AEs and SAEs CBR DoR ORR OS PFS TTP
Patritumab Deruxtecan with Other Anti-cancer Agents in Participants with HER2+ Breast Cancer that has Spread and cannot be Surgically Removed (MK-1022-009/HERTHENA-Breast-01)	NCT06686394	Ib/II	Not yet reruiting	Patritumab deruxtecan	HER3	Topoisomerase I inhibitor	8	Trastuzumab Pertuzumab Tucatinib	HER2 MAb HER2 and HER3 MAb TKI	Arm A: HER3-DXd + trastuzumab Arm B: HER3-DXd + pertuzumab + trastuzumab Arm C: HER3-DXd + trastuzumab + tucatinib	HER2+ locally advanced unresectable or metastatic breast cancer	DLTs AEs

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Table 2 (continued) | Representative ongoing clinical trials of ADC combination therapies in breast cancer

Name of Trial	NCT #	Phase	Status	ADC	ADC target antigen	ADC payload	DAR	Combination therapeutic	MOA	Study arms	Indication	Primary endpoint
Alpelisib And Sacituzumab Govitecan for Treatment of Breast Cancer (ASSET)	NCT05143229	I	Recruiting	Sacituzumab govitecan	TROP2	SN-38	7.6	Alpelisib	PIK3 inhibitor	Arm A: SG 8 mg/kg + alpelisib 250 mg Arm B: SG 10 mg/kg + alpelisib 250 mg Arm C: SG 10 mg/kg + alpelisib 300 mg	HER2-negative, including TNBC or HR +, locally advanced or metastatic	DLTs
Sacituzumab Govitecan-hziy and Pembrolizumab Versus TPC and Pembrolizumab in Patients with Previously Untreated, Locally Advanced Inoperable or Metastatic TNBC (ASCENT-04)	NCT05382286	III	Active, not recruiting	Sacituzumab govitecan	TROP2	SN-38	7.6	Pembrolizumab	PD-1 inhibitor	Arm A: SG + pembrolizumab Arm B: TPC (paclitaxel, nab-paclitaxel or gemcitabine + carboplatin) + pembrolizumab	PD-L1 positive TNBC, locally recurrent or metastatic	PFS
Sacituzumab Govitecan in Combination with Talazoparib in Patients with Metastatic Breast Cancer	NCT04039230	Ib/II	Recruiting	Sacituzumab govitecan	TROP2	SN-38	7.6	Talazoparib	PARP inhibitor	SG + talazoparib	Metastatic TNBC	DLTs
SAcituzumab Govitecan and Trastuzumab for HER2+ Metastatic Breast Cancer After Trastuzumab dEruxtEcaN (SATEEN)	NCT06100874	II	Recruiting	Sacituzumab govitecan	TROP2	SN-38	7.6	Trastuzumab	HER2 MAb	SG + trastuzumab (or biosimilar)	HER2+ metastatic breast cancer	ORR
Sacituzumab Tirumotecan (MK-2870) as a Single Agent and in Combination with Pembrolizumab Versus TPC in Participants With HR + / HER2- negative Unresectable Locally Advanced or Metastatic Breast Cancer (MK-2870-010/TroFuse-010)	NCT06312176	III	Recruiting	Sacituzumab tirumotecan (MK-2870)	TROP2	Topoisomerase I inhibitor	7.4	Pembrolizumab	PD-1 inhibitor	Arm A: MK-2870 Arm B: MK-2870 + pembrolizumab Arm C: TPC (paclitaxel, nab-paclitaxel, capecitabine, or liposomal doxorubicin)	HR + /HER2- negative unresectable locally advanced or metastatic breast cancer	PFS
ADCs Combined with Adebrelimab in HER2-negative Advanced Breast Cancer	NCT06433609	II	Not Yet Recruiting	SHR1811 SHR1921	HER2 TROP2	Topoisomerase I inhibitor Topoisomerase I inhibitor	5.7 4	Adebrelimab	PD-L1 inhibitor	Arm A: SHR-A1811 + adebrelimab Arm B: SHR-A1921 + adebrelimab	HER2-negative advanced breast cancer	ORR
Anlotinib With Trastuzumab Deruxtecan for Previously Treated HER2-Low Advanced Breast Cancer (ALTER-BC-Ib-01)	NCT06331169	Ib	Recruiting	Trastuzumab deruxtecan	HER2	Topoisomerase I inhibitor	8	Anlotinib	TKI	Arm A: T-DXd + anlotinib 8 mg Arm B: T-DXd + anlotinib 10 mg Arm C: T-DXd + anlotinib 12 mg	HER2 low expression (HR +/-) advanced (unresectable or metastatic) breast cancer	ORR RP2D

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Table 2 (continued) | Representative ongoing clinical trials of ADC combination therapies in breast cancer

Name of Trial	NCT #	Phase	Status	ADC	ADC target antigen	ADC payload	DAR	Combination therapeutic	MOA	Study arms	Indication	Primary endpoint
T-DXd Combinations in HER2+ Metastatic Breast Cancer (DESTINY-Breast07)	NCT04538742	Ib/II	Active, not recruiting	Trastuzumab deruxtecan	HER2	Topoisomerase I inhibitor	8	Durvalumab Pertuzumab Paclitaxel	PD-L1 inhibitor HER2 MAb Anti-microtubule	Arm A: T-DXd + durvalumab Arm B: T-DXd + pertuzumab Arm C: T-DXd + paclitaxel Arm D: T-DXd + durvalumab + paclitaxel Arm E: T-DXd monotherapy Arm F: T-DXd + tucatinib Arm G: T-DXd + tucatinib (with active brain mets) Arm H: T-DXd monotherapy (with active brain mets)	HER2+ locally advanced (unresectable) metastatic breast cancer	AEs and SAEs
Testing the Safety and Tolerability of the Anti-cancer Drugs Trastuzumab Deruxtecan and Neratinib for Cancers with Changes in the HER2 Gene	NCT05372614	I	Suspended	Trastuzumab deruxtecan	HER2	Topoisomerase I inhibitor	8	Neratinib	TKI	T-DXd + neratinib	HER2+ or mutated metastatic or unresectable solid tumor	AEs DLTs
DS8201a and Pembrolizumab in Participants with Locally Advanced/ Metastatic Breast or NSCLC	NCT04042701	Ib	Recruiting	Trastuzumab deruxtecan	HER2	Topoisomerase I inhibitor	8	Pembrolizumab	PD-1 inhibitor	Part 1: dose escalation Part 2: dose expansion in HER2 + BC (T-DXd + pembrolizumab) and in HER2 low-expression and in HER2-expressing and HER2-mutant NSCLC	HER2-expressing locally advanced/ metastatic breast and HER2-expressing or HER2-mutant locally advanced/ metastatic NSCLC	DLTs ORR
Trastuzumab Deruxtecan With or Without Pertuzumab Versus Taxane, Trastuzumab and Pertuzumab in HER2+ Metastatic Breast Cancer (DESTINY-Breast09)	NCT04784715	III	Active, not recruiting	Trastuzumab deruxtecan	HER2	Topoisomerase I inhibitor	8	Pertuzumab	HER2 MAb	Arm A: T-DXd + pertuzumab-matching placebo Arm B: T-DXd + pertuzumab Arm C: standard of care (taxane, trastuzumab, and pertuzumab)	HER2+ locally advanced or metastatic breast cancer	PFS
AZD5305 as Monotherapy and in Combination with Anti-cancer Agents in Patients with Advanced Solid Malignancies (PETRA)	NCT04644068	I/IIa	Recruiting	Trastuzumab deruxtecan Datopotamab deruxtecan	HER2 TROP2	Topoisomerase I inhibitor Topoisomeriase I inhibitor	8 4	Paclitaxel Carboplatin Camizestrant AZD5305	Anti-microtubule Platinum SERD PARP inhibitor	Arm A: AZD5305 monotherapy Arm B: AZD5305 + paclitaxel Arm C: AZD5305 + carboplatin +/- paclitaxel Arm D: AZD5305 + T-DXd Arm E: AZD5305 + Dato-DXd Arm F: AZD5305 + camizestrant	Advanced breast cancer and other solid tumors	AEs and SAEs DLTs
BEGONIA: Durvalumab combinations in locally advanced/ metastatic TNBC	D933LC00001	Ib/II	Active, not recruiting	Trastuzumab deruxtecan Datopotamab deruxtecan	HER2 TROP2	Topoisomerase I inhibitor Topoisomerase I inhibitor	8 4	Paclitaxel Capivasertib Oleclumab	Anti-microtubule AKT inhibitor Anti-CD73 MAb	Arm 6: Durvalumab + T-DXd Arm 7: Durvalumab + Dato-DXd Arm 8: Durvalumab + Dato-DXd (patients with PD-L1 positive status)	Locally advanced/ metastatic TNBC	AEs
4-1BB Agonist Monoclonal Antibody PF-05082566 With Trastuzumab Emtansine or Trastuzumab in Treating Patients with Advanced HER2+ Breast Cancer	NCT03364348	I	Completed	Trastuzumab deruxtecan Trastuzumab emtansine	HER2 HER2	Topoisomerase I inhibitor DM1	8 3.5	Utomilumab	4-1BB/ CD137 receptor agonist	Arm 1 A: T-DXd 6 mg/kg + utomilumab 20 mg Arm 1B: T-DXd 6 mg/kg + utomilumab 100 mg Arm 2 A: T-DM1 3.6 mg/kg + utomilumab 20 mg Arm 2B: T-DM1 3.6 mg/kg + utomilumab 100 mg	HER2+ locally advanced (unresectable) or metastatic breast cancer	DLTs

Table 2 (continued) | Representative ongoing clinical trials of ADC combination therapies in breast cancer

Name of Trial	NCT #	Phase	Status	ADC	ADC target antigen	ADC payload	DAR	Combination therapeutic	MOA	Study arms	Indication	Primary endpoint
T-DM1 With Abraxane and Lapatinib for Metastatic HER2+ Breast Cancer (STELA)	NCT02073916	Ib	Completed	Trastuzumab emtansine	HER2	DM1	3.5	Abraxane Laptinib	Anti-microtubule TKI	T-DM1 + lapatinib + abraxane	HER2 Neu overexpressed metastatic breast cancer	MTD
BYL719 + T-DM1 in HER2+ Metastatic Breast Cancer Patients Who Progress on Prior Trastuzumab & Taxane Treatment	NCT02038010	I	Completed	Trastuzumab emtansine	HER2	DM1	3.5	BYL719 (Alpelisib)	PIK3 inhibitor	BYL719 + trastuzumab emtansine	HER2+ locally advanced or metastatic breast cancer	DLTs MTD

NCT National Clinical Trial, *ADC* antibody-drug conjugate, *DAR* drug-to-antibody ratio, *MOA* mechanism of action, *TIGIT* T-cell immunoreceptor with immunoglobulin and tyrosine-based inhibitory motif, *PD-1* programmed cell death 1; BTC: biliary tract cancer, *AEs* adverse events, *SAEs* serious adverse events, *DLTs* dose limiting toxicities, *HER2* human epidermal growth factor receptor 2, *TLR7/8* toll-like receptor type 7 and 8, *MTD* maximum tolerated dose, *ORR* objective-response rate, *MAb* monoclonal antibody, *Dato-DXd* Datopotamab deruxtecan, *ICC* investigator's choice of chemotherapy, *PD-L1* programmed death-ligand 1, *TNBC* triple-negative breast cancer, *TROP2* trophoblast antigen 2, *PFS* progression-free survival, *MMAE* monomethyl auristatin E, *TKI* tyrosine kinase inhibitor, *RC48* Disitamab vedotin, *GE* gastroesophageal, *HR* hormone receptor, *DM1* derivative of maytansine 1, *Ab* antibody, *CBR* clinical benefit rate, *DoR* duration of response, *OS* overall survival, *TTP* time to progression, *HER3* human epidermal growth factor receptor 3, *HER3-DXd* patritumab deruxtecan, *SN-38* 7-ethyl-10-hydroxycamptothecin, *PIK3* phosphatidylinositol 3-kinase, *mg/kg* milligram/kilogram, *SG* sacituzumab govitecan, *TPC* treatment of physician's choice, *PARP* poly-ADP ribose polymerase, *MK-2870* sacituzumab tirumotecan, *T-DXd* trastuzumab deruxtecan, *RP2D* recommended phase 2 dose, *NSCLC* non-small cell lung cancer, *SERD* selective estrogen receptor degrader, *AKT* protein kinase B, *CD73* ecto-5′-nucleotidase, *4-1BB* CD137/cluster of differential 137, *T-DM1* trastuzumab emtansine.

trastuzumab (maximum standardized uptake value, SUV_{max}) was higher in patients with HER2-positive breast tumors when compared to those with HER2-negative tumors, particularly when hepatic metastatic lesions were excluded from the analysis. A similar trend in trastuzumab uptake in HER2-positive versus HER2-negative tumors was reported by Mortimer et al. using [^{64}Cu]DOTA-trastuzumab as the PET radiopharmaceutical[86]. Other clinical trials have evaluated HER2-targeted PET/CT in patients with breast tumors[87,88].

PET radiopharmaceuticals such as [^{89}Zr]trastuzumab show promise in assessing HER2 availability for binding to trastuzumab-based ADC therapies. This approach could guide personalized treatment by identifying patients who are most likely (or unlikely) to benefit from ADC therapy. A landmark study by Gebhart et al. evaluated ^{89}Zr-trastuzumab and FDG PET/CT in patients with HER2 overexpression treated with trastuzumab emtansine in the ZEPHIR trial[89,90]. ^{89}Zr-trastuzumab PET/CT was performed at baseline, and FDG PET/CT was performed at baseline and after cycle one of trastuzumab emtansine. By evaluating intra-patient heterogeneity and combining HER2-PET with FDG PET/CT, patients could be divided into two groups with differing outcomes of FDG-avid tumor load showing relevant [^{89}Zr]trastuzumab uptake. This study reinforced the potential to use imaging to assess heterogeneity within tumors and predict shorter responses to trastuzumab emtansine, despite all of these tumors having HER2 tissue overexpression based on pathological evaluation. Whether using these imaging findings to change therapy early on (e.g., after cycle one) would improve clinical outcomes is currently unknown. In a feasibility trial, it was demonstrated that in 15 of 20 patients ^{89}Zr-trastuzumab PET enabled assisting in clinical decision-making when HER2 status could not be determined by conventional approaches[91]. A similar approach using ^{64}Cu-trastuzumab PET/CT and traditional PET/CT evaluated patients at baseline prior to initiation of trastuzumab emtansine[92]. Baseline uptake as measured by SUV_{max} correlated with clinical response. Further studies are needed to evaluate these approaches at lower levels of HER2 expression and with newer ADCs.

The ZEPHIR-02 clinical trial (NCT06595563) is evaluating ^{89}Zr-trastuzumab PET/CT and FDG PET/CT as a tool for ADC sequencing. The trial plans to enroll patients with metastatic disease after progression on trastuzumab deruxtecan, and patients will be assessed using ^{89}Zr-trastuzumab PET/CT and FDG PET-CT to determine the probability of response to trastuzumab emtansine. Those with a high probability based on the majority of the tumor having tracer uptake as determined in the original ZEPHIR trial will receive trastuzumab emtansine, while those who are characterized as negative will receive therapy of the physician's choice. The primary endpoints include assessing genomic alterations, HER2 expression, and time to treatment failure.

The IMPACT study was an effort to evaluate the potential clinical utility of molecular imaging in treatment-decision making[93]. Two-hundred patients underwent [^{18}F]FDG-PET, [^{89}Zr]trastuzumab-PET (HER2-PET), [^{18}F]FES-PET, and early [^{18}F]FDG-PET after 2 weeks, along with biopsy of a metastatic site at baseline. There was a discrepancy between the tissue biopsy ER or HER2 subtyping and PET imaging in 26% of patients, and 41 of these 52 patients received treatment based on the PET imaging. PFS was 23.2 months in patients who were both HER2 positive based on IHC and PET, while only 4.5 months in those who were HER2 positive by IHC and negative by HER2-PET. Further, for patients who were HER2 negative by IHC but HER2 positive by HER2-PET, investigational HER2-targeted treatment led to a PFS of 11.4 months, highlighting the potential for molecular imaging to guide therapeutic decisions in the future. However, the production and availability of radiopharmaceuticals for cancer imaging vary across academic medical centers and countries, and this currently limits the broad clinical implementation of HER2-PET imaging[94].

Typically, HER2-PET trastuzumab-based radioimmunoconjugates are prepared by randomly attaching chelators to lysine residues within the antibody. These immunoconjugates are then labeled with a radiometal, such as ^{89}Zr. While random conjugation methods are straightforward, they often result in poorly defined products with suboptimal in vivo characteristics.

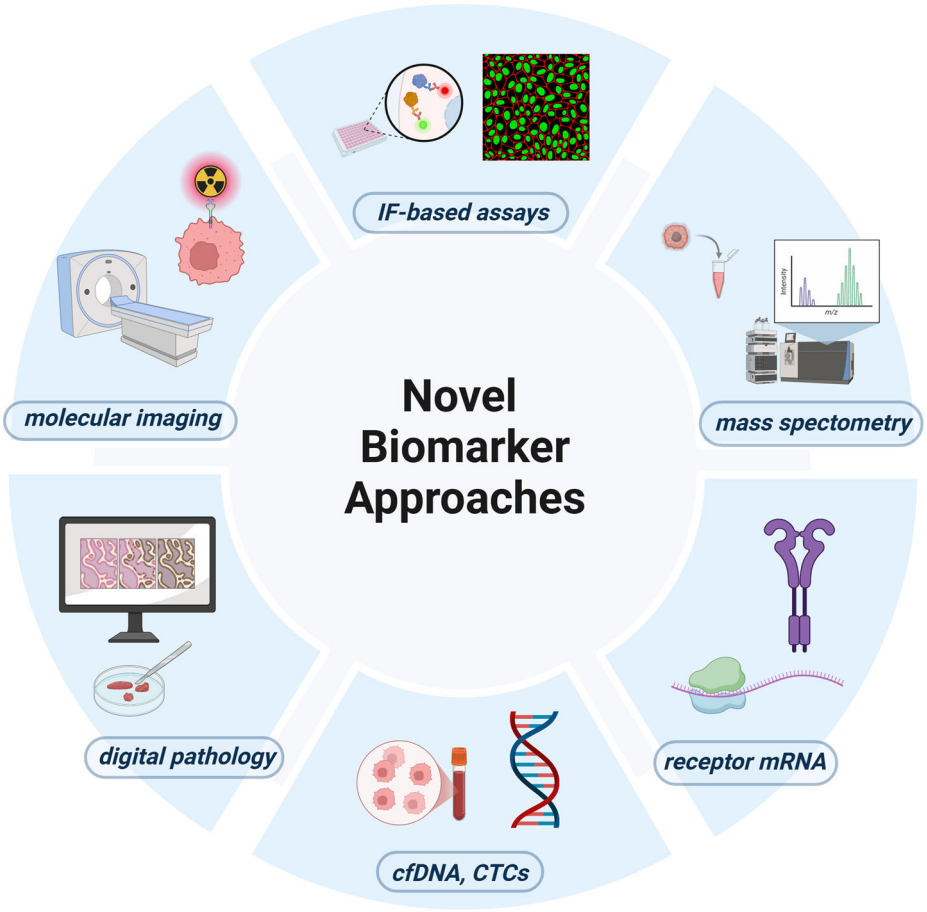

Fig. 1 | Ongoing clinical trials in the window of opportunity, neoadjuvant, and adjuvant settings for ADC therapy in early-stage breast cancer with associated primary end points. *TROPION-Breast04 is both in the neoadjuvant and adjuvant setting. CelTIL a combined biomarker based on tumor cellularity and tumor-infiltrating lymphocytes (TILs), pCR pathologic complete response, ORR objective-response rate, RCB residual cancer burden, ctDNA circulating tumor DNA, iDFS invasive disease-free survival, EFS event-free survival.

These can include diminished immunoreactivity and increased nonspecific uptake in off-target tissues, which can negatively impact the tracer's biodistribution. Recently, a site-specific modification approach for HER2 detection using ^{89}Zr-pertuzumab immunoPET has been reported[95]. Other PET radiopharmaceuticals evaluated in clinical settings include [^{18}F]FBEM-trastuzumab, [^{68}Ga]Ga-DOTA-F(ab′)$_2$-trastuzumab, [^{89}Zr]Zr-Df-HER2-Fab-PAS200, [^{18}F]GE266, and [^{68}Ga]Ga-ABY-025[96]. In particular, [^{68}Ga]Ga-ABY-025 has been investigated in both HER2-high and HER2-low breast cancer[97,98]. The potential for HER2 PET imaging to distinguish HER2-low tumors remains an active area of investigation.

Circulating biomarkers

Another promising approach is to utilize liquid biopsies including non-invasive circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs) to help identify patients for ADC therapy. The utility of this approach may depend on the drug target. As proof of principle, the HER-ALD/EPIC1806 trial evaluated the use of trastuzumab deruxtecan in patients with amplification of HER2 based on ctDNA testing without the requirement of IHC evaluation[99]. While the amplifications were only identified in a small subset of patients (252/4,734, 5.3%), ORR was high in this molecular-defined subset at 56.5% across a variety of tumor histologies. The degree of HER2 amplification based on ctDNA in patients with HER2 overexpression may also correlate with treatment response, and further studies have demonstrated *HER2* mutations as predictors of response to trastuzumab deruxtecan in both ctDNA and tissue[100,101]. HER2 expression can also be characterized on CTCs and may be discordant with tissue expression of HER2. Several studies have demonstrated the capability to detect and capture HER2-positive CTCs in a variety of settings, although how this impacts clinical management is currently unknown[102]. A summary of biomarker approaches is shown in Fig. 1.

Collectively, novel biomarkers are necessary to more accurately characterize the therapeutic target in both the tumor and non-malignant tissues for optimal prediction of treatment response. Concurrent development of drugs and biomarkers for both response and toxicity is needed to optimize the therapeutic window of ADCs to improve targeted delivery of the payload and limit off-target chemotherapeutic effects. A lack of well-defined biomarkers may lead to drugs with similar payloads, with uncertainty regarding the choice and sequencing of these agents. Current data suggest high rates of all grades and grade 3 or higher toxicities with ADCs, suggesting significant off-target effects[103]. This has led to ongoing efforts to evaluate predictors of ADC toxicity, including ILD/pneumonitis, ocular toxicity, mucositis, and diarrhea. However, at present, no strategies are ready for implementation into clinical practice for optimal selection of ADCs with similar mechanisms of action.

Moving ADCs to the early-stage setting

While the enhanced efficacy of ADCs compared to conventional chemotherapy in the metastatic setting is promising, there are clear opportunities and challenges for drug development to transition ADCs to the early-stage setting. First, the long-term safety and efficacy of both monotherapy and combination therapies need to be defined. Second, serious, potentially fatal, and toxicities that significantly impair quality of life need to be carefully monitored, such as ILD/pneumonitis and ocular toxicity, and holding therapy indefinitely may have significant implications in the curative-intent setting. Third, the benchmarks for effective outcomes, particularly in the neoadjuvant setting for patients with TNBC and HER2+ early-stage breast cancer, are high, and surpassing these, or achieving similar outcomes with decreased short and long-term toxicities, warrants thoughtful clinical trial designs. Current clinical trials have explored ADCs in window-of-opportunity studies using biomarker-defined endpoints, in the

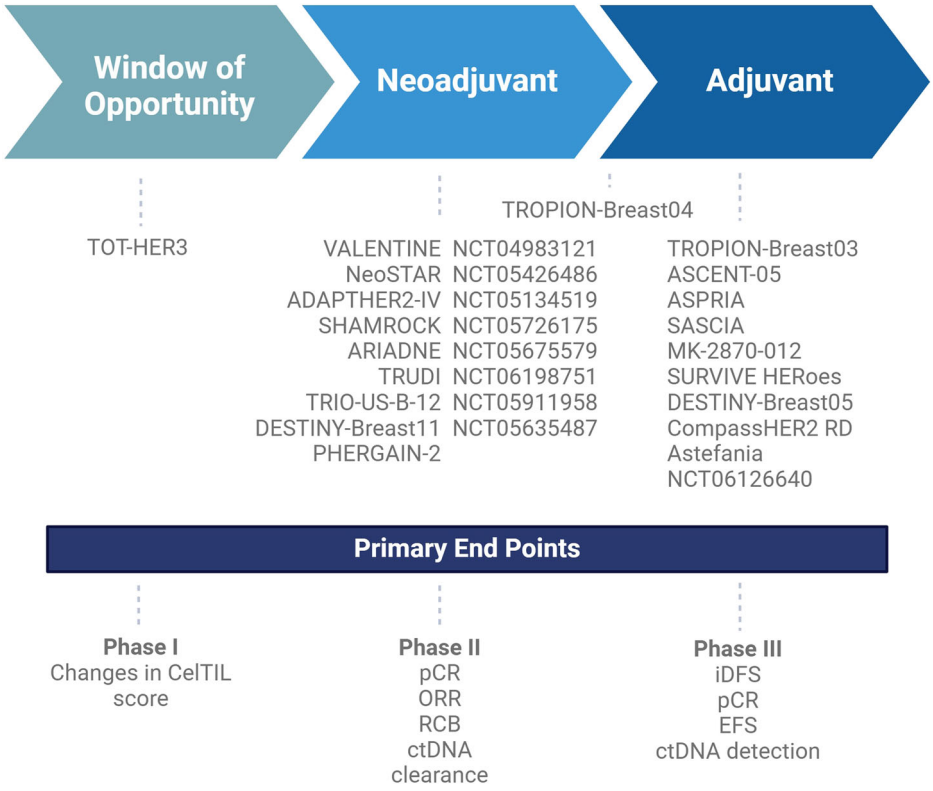

Fig. 2 | Overview of the novel biomarker approaches in development to aid in tumor characterization for optimization of ADC therapy. mRNA messenger ribonucleic acid, cfDNA cell-free deoxyribonucleic acid, CTCs circulating tumor cells.

neoadjuvant setting with pathological complete response (pCR) rate as the most common primary endpoint, and utilization of ADCs in the postoperative setting, as defined by non-pCR, with the goal of improving outcomes in patients with the highest risk of recurrence (Fig. 2).

HER2

The first study to demonstrate that an ADC can improve outcomes in the adjuvant setting was the KATHERINE trial, which demonstrated an improvement with trastuzumab emtansine compared to trastuzumab and pertuzumab in HER2-positive patients with residual disease after neoadjuvant therapy[2]. Trastuzumab emtansine was subsequently evaluated in the phase II WSG-ADAPT-TP trial comparing trastuzumab emtansine with or without endocrine therapy and trastuzumab with endocrine therapy for patients with early-stage HR + /HER2+ breast cancer[104]. The rationale of the study was to avoid conventional chemotherapy with a taxane and carboplatin. All three arms that were evaluated had statistically similar invasive disease-free survival (iDFS) and OS at 5 years. This clinical trial reinforces that biomarkers are needed to evaluate the optimal regimens in individual patients to better understand the risk, immunogenicity, and mutational profile of patients who would benefit from an ADC-based therapeutic approach versus monoclonal antibody alone.

SHR-A1811, as previously discussed, was evaluated as monotherapy and combined with a tyrosine kinase inhibitor for patients with Stage II and III HER2+ breast cancer (NCT05582499)[105]. Two-hundred sixty-five patients were assessed across three study arms, including SHR-A1811 monotherapy for 8 cycles, SHR-A1811 with pyrotinib for 8 cycles, and standard-of-care chemotherapy with trastuzumab and pertuzumab with pCR as the primary endpoint. All three arms had similar pCR rates, ranging from 62–66%, and there was no statistically significant difference in pCR rate between the SHR-A1811 monotherapy (63%) versus SHR-A1811 plus pyrotinib (62%) arms. Grade 3 or higher toxicity was present in 45% of patients who received SHR-A1811 versus 34% in the standard-of-care arm, with only one patient having ILD/pneumonitis with the ADC, with a drug discontinuation rate of 5.7% with SHR-A1811 versus 29.9% with the ADC in combination. These data indicate the potential for a single ADC to achieve similar outcomes to standard-of-care combination strategies.

HER3

In the SOLTI TOT-HER3 study, patritumab deruxtecan was explored in patients with HR + HER2- breast cancer in a window-of-opportunity study[106,107]. The study consisted of multiple arms based on ERBB3 messenger RNA expression with all patients receiving a single dose of the drug. The primary objective was to assess tumor cellularity and tumor-infiltrating lymphocytes, and this endpoint was met to demonstrate enhanced immune infiltration. However, even with a single dose of patritumab deruxtecan, 96% of patients experienced a treatment-emergent adverse event, and 14% of patients experienced a grade 3 or higher toxicity event, which reinforces that toxicity was common and severe in some patients. In part B of the study, which consisted of further evaluation of the subset of patients who received patritumab deruxtecan at 5.6 mg/kg (44/98, 44.9%), an inverse relation was reported for HER2DX *ERBB2* mRNA expression and HER2-DXd activity[107]. The SOLTI-2103 VALENTINE trial (NCT05569811) evaluated patritumab deruxtecan with or without letrozole versus chemotherapy in the neoadjuvant setting in a randomized, non-comparative study (Arm A: patritumab deruxtecan 5.6 mg/kg for 6 cycles, Arm B: patritumab deruxtecan with letrozole +/- LHRH agonist, and Arm C: anthracycline-based chemotherapy regimens with a taxane) with the primary endpoint as pCR rate[108]. Patients with early-stage HR + HER2- breast cancer were enrolled with Ki67 of at least 20% and/or high genomic risk profiles. pCR rates were 4.0%, 2.1%, and 4.2% in Arms A, B, and C, respectively. Grade 3 or higher toxicity was lower in the arms that received the ADC (less than 20%) versus 54.2% in Arm C. Improved biomarkers and/or novel combination strategies will be needed to improve pCR in this setting.

TROP2

Sacituzumab govitecan was evaluated in patients with early-stage TNBC in the NeoSTAR trial[109]. Fifty patients were enrolled and received four cycles of therapy. Importantly, all but one patient completed the protocol-defined therapy with an overall pCR rate of 30%. Twenty-nine patients proceeded

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Table 3 | Representative ongoing clinical trials of ADCs in the window of opportunity, neoadjuvant, and adjuvant settings for early-stage breast cancer

Name of Trial	NCT #	Phase	Status	ADC	ADC target antigen	ADC payload	Study arms	Setting	Indication	Primary endpoint
A Window-of-opportunity Study of U3-1402, a HER3-targeting ADC in Operable Breast Cancer According to ERBB3 Expression (TOT-HER3)	NCT04610528	I	Active, not recruiting	Patritumab deruxtecan	HER3	Topoisomerase I inhibitor	Arm A: HER3-DXd at 6.4 mg/kg Arm B: HER3-DXd at 5.6 mg/kg	Window of opportunity	HR+/HER2-negative early breast cancer	Changes in CelTIL score
Pyrotinib Maleate Combined with ARX788 Neoadjuvant Treatment in Breast Cancer Patients	NCT04983121	II	Recruiting	Anvatabart opadotin (ARX788)	HER2	MMAF	ARX788 + pyrotinib maleate for 6 sessions	Neoadjuvant	HER2+ breast cancer, stage II-III	RCB
ARX788 Combined with Pyrotinib Maleate Versus TCBHP (Trastuzumab Plus Pertuzumab with Docetaxel and Carboplatin) as Neoadjuvant Treatment in HER2+ Breast Cancer Patients	NCT05426486	II/III	Active, not recruiting	Anvatabart opadotin (ARX788)	HER2	MMAF	Arm A: ARX788 + pyrotinib maleate for 6 cycles Arm B: TCBHP (trastuzumab + pertuzumab + docetaxel + carboplatin) for 6 cycles	Neoadjuvant	HER2+ breast cancer, stage II-III	pCR
RC48 for Neoadjuvant Chemotherapy of HER2+ Breast Cancer	NCT05134519	II	Not yet recruiting	Disitamab vedotin (RC48)	HER2	MMAE	RC48 for 4-6 cycles	Neoadjuvant	HER2 +, early or locally advanced breast cancer	pCR
Disitamab Vedotin Combined with Penpulimab for Neoadjuvant Treatment of HER2-low Breast Cancer	NCT05726175	II	Not yet recruiting	Disitamab vedotin (RC48)	HER2	MMAE	RC48 + penpulimab for 6 cycles	Neoadjuvant	HER2-low breast cancer, clinical stage II-III	pCR
NeoadjuVAnt muLti-agENT Chemotherapy or Patritumab Deruxtecan with or Without endocrINE Therapy for High-risk HR + / HER2-negative Breast Cancer - VALENTINE Trial (VALENTINE)	NCT05569811	II	Completed	Patritumab deruxtecan	HER3	Topoisomerase I inhibitor	Arm A: HER3-DXd + endocrine therapy Arm B: HER3-DXd monotherapy Arm C: Anthracycline/taxane-based neoadjuvant regimen	Neoadjuvant	HR + /HER2-negative breast cancer	pCR
Sacituzumab Govitecan In TNBC (NeoSTAR)	NCT04230109	II	Recruiting	Sacituzumab govitecan	TROP2	SN-38	Arm A: SG for 4 cycles Arm B: SG + pembrolizumab for 4 cycles	Neoadjuvant	Non-metastsatic TNBC	pCR
Neoadjuvant Sacituzumab Govitecan and Pembrolizumab Therapy for Immunochemotherapy-resistant Early-stage TNBC	NCT05675579	II	Recruiting	Sacituzumab govitecan	TROP2	SN-38	SG + pembrolizumab for 4 cycles	Neoadjuvant	Early-stage TNBC	pCR
Neoadjuvant Treatment with TQB2102 for Injection for HER2+ Breast Cancer	NCT06198751	II	Recruiting	TQB2102	HER2	Topoisomerase I inhibitor	Arm A: TQB2102 6 mg/kg for 6 or 8 cycles Arm B: TQB2102 7.5 mg/kg for 6 or 8 cycles	Neoadjuvant	HER2+ breast cancer	pCR

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Table 3 (continued) | Representative ongoing clinical trials of ADCs in the window of opportunity, neoadjuvant, and adjuvant settings for early-stage breast cancer

Name of Trial	NCT #	Phase	Status	ADC	ADC target antigen	ADC payload	Study arms	Setting	Indication	Primary endpoint
NeoAdjuvant Therapy with Trastuzumab-deruxtecan Versus Chemotherapy +Trastuzumab +Pertuzumab in HER2+ Early Breast Cancer (ADAPTHER2-IV)	NCT05704829	II	Recruiting	Trastuzumab deruxtecan	HER2	Topoisomerase I inhibitor	Arm A: T-DXd for 12 weeks in HER2+ and low-intermediate risk for recurrence group (and pCR dependent T-DXd for 1 year post-neoadjuvant) Arm B: T-DXd for 18 weeks in HER2+ and intermediate-high risk for recurrence group (and pCR dependent T-DXd for 1 year post-neoadjuvant) Comparator: Standard of care for both groups	Neoadjuvant	HER2+ early-stage breast cancer	pCR
Neoadjuvant Trastuzumab Deruxtecan with Response-directed Definitive Therapy in Early-Stage HER2+ Breast Cancer (SHAMROCK Study)	NCT05710666	II	Active, not recruiting	Trastuzumab deruxtecan	HER2	Topoisomerase I inhibitor	T-DXd for up to 6 cycles	Neoadjuvant	HER2+ early-stage breast cancer	pCR
Trastuzumab Deruxtecan Versus Standard Neoadjuvant Treatment for HER2+ Breast Cancer (ARIADNE)	NCT05900206	II	Recruiting	Trastuzumab deruxtecan	HER2	Topoisomerase I inhibitor	Arm A: T-DXd for 3 courses Arm B: Standard treatment (TCHP or PCHP) for 3 cycles Arm C: Ribociclib, letrozole, trastuzumab, and pertuzumab for cycles 4-6 in ER+ and luminal BC Arm D: Epirubicin and cyclophosphamide if no rCR after 3 cycles for cycles 4-6, or T-DXd or TCHP/PCHP for cycles 4-6 if rCR in ER- and luminal, or basal-like, or normal-like BC Arm E: T-DXd or TCHP/PCHP for cycles 4–6 for HER2-enriched BC	Neoadjuvant	HER2+ non-metastatic breast cancer	pCR
TRUDI: T-DXd+Durva in HER2 + / low IBC (TRUDI)	NCT05795101	II	Recruiting	Trastuzumab deruxtecan	HER2	Topoisomerase I inhibitor	Arm A: T-DXd + durvalumab in HER2+ patients Arm B: T-DXd + durvalumab in HER2-low patients	Neoadjuvant	HER2+ stage III inflammatory breast cancer	pCR
TRIO-US B-12 TALENT: Neoadjuvant trial evaluating trastuzumab deruxtecan with or without anastrozole for HER2-low, HR+ early-stage breast cancer	NCT04553770	II	Recruiting	Trastuzumab deruxtecan	HER2	Topoisomerase I inhibitor	Arm A: T-DXd for 6–8 cycles Arm B: T-DXd + anastrozole for 6-8 cycles	Neoadjuvant	HER2-low, HR + early-stage breast cancer	pCR
Neoadjuvant T-DXd Monotherapy or T-DXd Followed by THP Compared to ddAC-THP in Participants with High-risk HER2+ Early-stage Breast Cancer (DESTINY-Breast11)	NCT05113251	III	Active, not recruiting	Trastuzumab deruxtecan	HER2	Topoisomerase I inhibitor	Arm A: T-DXd Arm B: T-DXd, followed by THP Arm C: Doxorubicin and cyclophosphamide, followed by THP	Neoadjuvant	High-risk, HER2+ early stage, non-metastatic breast cancer	pCR
Chemotherapy-Free pCR-Guided Strategy with Trastuzumab-pertuzumab and T-DM1 in HER2+ Early Breast Cancer (PHERGAIN-2)	NCT04733118	II	Active, not recruiting	Trastuzumab emtansine	HER2	DM1	Trastuzumab + pertuzumab (FDC SC) and T-DM1 (+ /- ET depending on HR status) for 3 cycles, followed by surgery within 4 weeks, followed by adjuvant systemic therapy with the following cohorts: Cohort A: PH FDC SC ± ET for 10 additional 3-week cycles Cohort B: T-DM1 ± ET for 10 cycles Cohort C: T-DM1 ± ET for 10 cycles, with possibility of PCC before adjuvant T-DM1	Neoadjuvant	HER2+ early-stage breast cancer	3y-RFI Global health status decline

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Table 3 (continued) | Representative ongoing clinical trials of ADCs in the window of opportunity, neoadjuvant, and adjuvant settings for early-stage breast cancer

Name of Trial	NCT #	Phase	Status	ADC	ADC target antigen	ADC payload	Study arms	Setting	Indication	Primary endpoint
SHR-A1811 as Neoadjuvant Treatment for Patients With HR+, HER2-Low Expression Breast Cancer	NCT05911958	II	Recruiting	Trastuzumab rezetecan (SHR-A1811)	HER2	Topoisomerase I inhibitor	SHR-A1811 for 8 cycles	Neoadjuvant	HR+/HER2-low expression breast cancer	ORR
SHR-A1811 Monotherapy or Combined with Pyrotinib Maleate as Neoadjuvant Treatment in HER2+ Breast Cancer Patients	NCT05635487	II	Completed	Trastuzumab rezetecan (SHR-A1811)	HER2	Topoisomerase I inhibitor	Arm A: SHR-A1811 monotherapy for 6 cycles Arm B: SHR-A1811 + pyrotinib for 6 cycles	Neoadjuvant	HER2+ stage II-III breast cancer	pCR
Dato-DXd and Durvalumab for Neoadjuvant/ Adjuvant Treatment of TN or HR-low/ HER2-negative Breast Cancer (TROPION-Breast04)	NCT06112379	III	Recruiting	Datopotamab deruxtecan	TROP2	Topoisomerase I inhibitor	Arm A: Neoadjuvant Dato-DXd + durvalumab, followed by 9 cycles of adjuvant durvalumab Arm B: Neoadjuvant pembrolizumab + chemotherapy, followed by 9 cycles of adjuvant pembrolizumab	Neoadjuvant Adjuvant	TN or HR-low/ HER2-negative breast cancer	pCR EFS
Dato-DXd With or Without Durvalumab Versus ICT in Patients with Stage I-III TNBC Without pCR Following Neoadjuvant Therapy (TROPION-Breast03)	NCT05629585	III	Recruiting	Datopotamab deruxtecan	TROP2	Topoisomerase I inhibitor	Arm A: Dato-DXd for 8 cycles + durvalumab for 9 cycles Arm B: Dato-DXd alone for 8 cycles Arm C: ICT (capecitabine, pembro, or capecitabine + pembro)	Adjuvant	Stage I-III TNBC without pCR following neoadjuvant therapy	iDFS
Sacituzumab Govitecan-hziy and Pembrolizumab Versus TPC in Patients with TNBC Who Have Residual Invasive Disease After Surgery and Neoadjuvant Therapy (ASCENT-05/ AFT-65 OptimICE-RD/ NSABP B-63)	NCT05633654	III	Recruiting	Sacituzumab govitecan	TROP2	SN-38	Arm A: SG + pembrolizumab for 8 cycles Arm B: TPC (pembrolizumab or pembrolizumab + capecitabine) for 8 cycles	Adjuvant	TNBC in breast or LNs after neoadjuvant therapy and surgery	iDFS
Atezolizumab + Sacituzumab Govitecan to Prevent Recurrence in TNBC (ASPRIA)	NCT04434040	II	Active, not recruiting	Sacituzumab govitecan	TROP2	SN-38	SG + atezolizumab for 6 cycles	Adjuvant	TNBC	ctDNA clearance
Sacituzumab Govitecan in Primary HER2-negative Breast Cancer (SASCIA)	NCT04595565	III	Active, not recruiting	Sacituzumab govitecan	TROP2	SN-38	Arm A: SG for 8 cycles Arm B: TPC (capecitabine or platinum-based chemo for 8 cycles, or observation)	Adjuvant	HER2-negative breast cancer with residual disease after neoadjuvant chemo	iDFS
Sacituzumab Tirumotecan (MK-2870) Plus Pembrolizumab Versus TPC in TNBC Who Did Not Achieve pCR (MK-2870-012)	NCT06393374	III	Recruiting	Sacituzumab tirumotecan (MK-2870)	TROP2	Topoisomerase I inhibitor	Arm A: MK-2870 + pembrolizumab for 24 weeks Arm B: TPC (pembrolizumab +/- capecitabine for 24 weeks)	Adjuvant	TNBC who did not achieve pCR	iDFS

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Table 3 (continued) | Representative ongoing clinical trials of ADCs in the window of opportunity, neoadjuvant, and adjuvant settings for early-stage breast cancer

Name of Trial	NCT #	Phase	Status	ADC	ADC target antigen	ADC payload	Study arms	Setting	Indication	Primary endpoint
A Randomized Secondary Adjuvant Treatment Intervention Study Comparing Trastuzumab Deruxtecan to SOC Therapy in EBC Patients with Molecular Relapse (SURVIVE HERoes)	NCT06643585	III	Not yet recruiting	Trastuzumab deruxtecan	HER2	Topoisomerase I inhibitor	Arm A: T-DXd 5.4 mg/kg + endocrine therapy for 16 cycles Arm B: TPC (ET, CDK4/6-inhibition, T-DM1, olaparib, trastuzumab, pertuzumab, capecitabine, or neratinib)	Adjuvant	HER2+ or HER2-low early breast cancer, intermediate to high-risk with molecular relapse	ctDNA clearance
Trastuzumab Deruxtecan Versus Trastuzumab Emtansine in High-risk HER2+Participants with Residual Invasive Breast Cancer Following Neoadjuvant Therapy (DESTINY-Breast05)	NCT04622319	III	Active, not recruiting	Trastuzumab deruxtecan Trastuzumab emtansine	HER2 HER2	Topoisomerase I inhibitor DM1	Arm A: T-DXd Arm B: T-DM1	Adjuvant	High-risk HER2+ breast cancer with residual disease after neoadjuvant therapy	iDFS
T-DM1 and Tucatinib Compared With T-DM1 Alone in Preventing Relapses in People with High-Risk HER2+ Breast Cancer (CompassHER2 RD)	NCT04457596	III	Recruiting	Trastuzumab emtansine	HER2	DM1	Arm A: T-DM1 + placebo for 14 cycles Arm B: T-DM1 + tucatinib for 14 cycles	Adjuvant	HER2+ breast cancer, high-risk	iDFS
Adjuvant Atezolizumab or Placebo and Trastuzumab Emtansine for Participants with HER2+ Breast Cancer at High Risk of Recurrence Following Preoperative Therapy (Astefania)	NCT04873362	III	Recruiting	Trastuzumab emtansine	HER2	DM1	Arm A: T-DM1 + placebo for 14 cycles Arm B: T-DM1 + atezolimab for 14 cycles	Adjuvant	HER2+ non-metastatic breast cancer	iDFS
SHR-A1811 Versus Trastuzumab Emtansine in HER2+ Primary Breast Cancer Participants with Residual Invasive Disease Following Neoadjuvant Therapy	NCT06126640	III	Not yet recruiting	Trastuzumab rezetecan	HER2	Topoisomerase I inhibitor	Arm A: SHR-A1811 Arm B: T-DM1	Adjuvant	HER2+ invasive, non-metastatic breast cancer	iDFS

NCT National Clinical Trial, *ADC* Antibody-drug conjugate, *HER3* human epidermal growth factor receptor 3, *ERBB3* erb-b2 receptor tyrosine kinase 3, *HER3-DXd* patritumab deruxtecan, *mg/kg* milligram per kilogram, *HR* hormone receptor, *HER2* human epidermal growth factor receptor 2, *CelTIL* a combined biomarker based on tumor cellularity and tumor-infiltrating lymphocytes (TILs), *ARX788* anvatabart opadotin, *MMAF* monomethyl auristatin F, *RCB* residual cancer burden, *TCBHP* trastuzumab plus pertuzumab with docetaxel and carboplatin, *pCR* pathologic complete response, *RC48* disitamab vedotin, *MMAE* monomethyl auristatin E; HR: hormone receptor; TNBC: triple-negative breast cancer; TROP2: trophoblast antigen 2; SN-38: 7-ethyl-10-hydroxycamptothecin; SG: Sacituzumab govitecan, *T-DXd* trastuzumab deruxtecan, *TCHP* docetaxel, carboplatin, trastuzumab, pertuzumab, *PCHP* paclitaxel, carboplatin, trastuzumab, pertuzumab, *ER* estrogen receptor, *BC* breast cancer, *rCR* radiologic complete response, *IBC* inflammatory breast cancer, *THP* paclitaxel, trastuzumab, pertuzumab, *ddAC* dose-dense doxorubicin and dose-dense cyclophosphamide, *T-DM1* trastuzumab emtansine, *DM1* derivative of maytansine 1, *FDC SC* fixed-dose subcutaneous, *ET* endocrine therapy, *PH FDC SC* trastuzumab + pertuzumab as a fixed-dose subcutaneous combination, *PCC* physician's choice of chemotherapy, *3y-RFI* 3-year recurrence-free interval, *SHR-A1811* trastuzumab rezetecan, *ORR* objective-response rate, *Dato-DXd* datopotamab deruxtecan, *TN* triple-negative, *EFS* event-free survival, *ICT* investigator's choice of therapy, *iDFS* invasive disease-free survival, *TPC* treatment of physician's choice, *SG* sacituzumab govitecan, *LN* lymph node, *ctDNA* circulating tumor DNA, *MK-2870* sacituzumab tirumotecan, *SOC* standard of care, *EBC* early breast cancer.

with surgery after the four cycles, while 21 participants received additional neoadjuvant chemotherapy. At two years of follow-up, event-free survival (EFS) was 95%. Further follow-up is needed to determine whether pCR is a predictor of long-term outcomes in this setting, and biomarkers are needed to define the subset of patients who achieved pCR with sacituzumab govitecan alone.

In the I-SPY2.2 phase 2 trial, datopotamab-deruxtecan was evaluated in combination with durvalumab in the neoadjuvant setting[110]. The I-SPY clinical trial platform utilizes tissue and MRI biomarkers to evaluate patients who may proceed to surgery with a high likelihood of pCR versus those who may benefit from additional neoadjuvant therapy. In this trial, 106 patients were evaluated who received this combination therapy, with 42 (39.6%) proceeding to surgery after datopotamab deruxtecan and pembrolizumab, and of the remaining 64 patients, 39 had surgery after taxane therapy and 25 after an anthracycline and cyclophosphamide. The most promising signal was observed in patients who were HER2 negative with an immune-enriched subtype, and additionally, 39% achieved a pCR in patients who were HR negative, HER2 negative, immune negative, and DNA repair deficiency negative. A total of six patients (5.7%) had grade 3 or 4 stomatitis, and three had pneumonitis. Their data highlight the potential to achieve relatively high pCR rates in an iterative, biomarker-driven neoadjuvant clinical trial with an ADC combined with immune checkpoint inhibition. The TROPION-Breast04 (NCT06112379) is currently evaluating 8 cycles of datopotomab deruxtecan with durvalumab compared to pembrolizumab, carboplatin, paclitaxel, followed by pembrolizumab, cyclophosphamide combined with an anthracycline (doxorubicin or epirubicin). The primary endpoints are pCR and EFS with the goal of potentially establishing a new neoadjuvant treatment regimen for patients with early-stage TNBC.

Ongoing trials

Multiple studies are ongoing in the neoadjuvant and/or adjuvant settings (Table 3). An active area of research is clinical trials evaluating ADCs in the adjuvant setting, particularly in patients with residual disease after neoadjuvant therapy. SASCIA (NCT04595565) is a phase III randomized trial comparing sacituzumab govitecan versus therapy of physician's choice in patients who are HER2 negative with defined thresholds for residual disease that differ based on whether the patient is HR + HER2 negative versus TNBC. OptimICE-RD is randomizing patients with residual TNBC after neoadjuvant therapy and surgery to sacituzumab govitecan and pembrolizumab for 8 cycles versus therapy of the physician's choice or pembrolizumab and capecitabine[111]. TROPION-Breast03 (NCT05629585) is evaluating datopotamab deruxtecan with or without durvalumab in patients with TNBC with residual disease after neoadjuvant therapy. The comparator group is standard-of-care therapy with a 2:1:2 randomization of datopotamab deruxtecan for 8 cycles and durvalumab for 9 cycles: datopotamab deruxtecan monotherapy: capecitabine, pembrolizumab, or the combination. In addition, sacituzumab tirumotecan (MK-2870) combined with pembrolizumab is being combined with pembrolizumab in patients with TNBC and residual disease in a phase 3 trial (NCT006393374).

Conclusions

We are currently at an inflection point of demonstrating how ADCs will revolutionize the way we treat patients with breast cancer in both the early-stage and advanced settings. Identifying multiple therapeutic targets and tumor vulnerabilities will be critical, along with improving the therapeutic window, optimizing the linker technology associated with ADCs to limit off-target toxicities from the chemotherapeutic payload, and better defining the threshold of antigen expression required for an effective ADC response. Furthermore, rational combination strategies based on characterization of synergistic mechanisms of action with non-overlapping primary toxicities will limit therapeutic resistance and extend the duration of response. Further research is needed to define whether this may occur via the administration of two separate ADCs with different payloads or a single ADC with dual payloads. Finally, in the era of precision oncology, biomarkers for cell surface target expression and tumor heterogeneity at the time of ADC selection and serially using non-invasive approaches, including liquid biopsy and novel imaging technologies, will enhance our ability to deliver these highly promising drugs to patients in the optimal clinical scenario.

Data availability

No datasets were generated or analyzed during the current study.

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Author contributions

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Competing interests

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Additional information

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