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Review Article

Therapies of Breast Cancer by Antibody-Drug Conjugates

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ABSTRACT

Breast cancer remains the most common malignancy in women globally, representing a significant clinical challenge despite recent therapeutic advances. Antibody-drug conjugates (ADCs) represent a paradigm shift in targeted cancer therapy, combining the specificity of monoclonal antibodies with the cytotoxic potency of chemotherapeutic agents. This review examines the current landscape of ADC-based therapies for breast cancer, encompassing mechanistic principles, clinically approved agents, and emerging therapeutic strategies. Trastuzumab deruxtecan (T-DXd/Enhertu) has demonstrated superior efficacy compared to first- generation ADCs in HER2-positive breast cancer, while sacituzumab govitecan (SG/Trodelvy) represents the first Trop-2-directed ADC with clinical efficacy in triple-negative breast cancer. Recent evidence extends ADC applications to HER2-low expressing tumors, expanding treatment populations. Key technical innovations including linker chemistry, payload optimization, and bystander effect mechanisms have enhanced ADC therapeutic indices. Resistance mechanisms and toxicity management remain critical considerations. Future directions include combinations with immunotherapy, exploration of novel targets (Trop-2, B7H3, HER3), development of bispecific ADCs, and personalized approaches based on biomarker assessment. This comprehensive review synthesizes current knowledge on ADC biology, clinical efficacy, safety profiles, and emerging therapeutic opportunities that promise to expand treatment options and improve outcomes for diverse breast cancer populations.

INTRODUCTION

Breast Cancer Epidemiology and Clinical Burden

Breast cancer represents the most common malignancy in women worldwide, with estimated annual incidence exceeding 2.3 million cases and approximately 685,000 deaths globally[11]. In developed nations, breast cancer survival rates

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have improved substantially over recent decades due to earlier detection and therapeutic advances; however, metastatic breast cancer remains largely incurable with median overall survival ranging from 2-3 years despite multiple sequential therapies. Breast cancer heterogeneity, defined by hormone receptor (HR) and human epidermal growth factor receptor-2 (HER2) status, creates distinct biological subtypes requiring different therapeutic approaches. Approximately 15-20% of breast cancers display HER2 overexpression, nearly 70% are HR-positive/HER2-negative, and approximately 15% are triple-negative (lacking HR and HER2 expression)[12].

Historical Context of Breast Cancer Therapy

Early breast cancer treatments relied on surgery and radiation therapy. The discovery of estrogen receptor signaling led to development of endocrine therapies including tamoxifen, aromatase inhibitors, and selective estrogen receptor degraders. The identification of HER2 as an oncogenic driver in a subset of breast cancers revolutionized therapy with introduction of trastuzumab (Herceptin), a humanized anti-HER2 monoclonal antibody, in the 1990s.

Trastuzumab dramatically improved outcomes for HER2-positive patients, establishing targeted therapy as a cornerstone approach[13]. However, substantial proportions of patients develop resistance to trastuzumab through various mechanisms including HER2 pathway activation, alternative growth signaling pathways, and impaired immune-mediated tumor cell killing.

Triple-negative breast cancer, lacking HR and HER2 expression, historically offered limited targeted options, with chemotherapy remaining the primary systemic treatment. The poor prognosis of triple-negative disease, combined with rapid treatment resistance, created urgent clinical need for novel therapeutic approaches applicable to this aggressive subtype.

Principles of Antibody-Drug Conjugate Therapy

Antibody-drug conjugates represent a rational approach to targeted cancer therapy by exploiting antibody specificity to deliver cytotoxic payloads selectively to tumor cells while minimizing off-target toxicity. The ADC concept combines three essential components: (1) a monoclonal antibody recognizing tumor-associated antigens; (2) a cytotoxic payload (chemotherapeutic agent); and (3) a linker connecting antibody to payload[14]. Successful ADC design requires balancing several competing objectives including maximizing tumor-directed delivery while maintaining plasma stability, achieving efficient payload release at the target site while preventing premature systemic release, and optimizing drug-to-antibody ratio to enhance efficacy without compromising stability.

ADC mechanisms of action involve sequential steps: antibody-antigen binding on tumor cell surface, receptor-mediated endocytosis of the antibody-antigen complex, trafficking to acidic intracellular compartments (lysosomes/ endosomes), proteolytic or chemical cleavage of the linker, and release of cytotoxic payload that engages intracellular targets to induce cell death. Payload classes have included microtubule-disrupting agents (maytansinoids, auristatins), DNA- damaging agents (calicheamicins, duocarmycins), and more recently, topoisomerase I inhibitors[15].

ADC Targets in Breast Cancer

HER2, the primary target in most approved breast cancer ADCs, represents a receptor tyrosine kinase overexpressed in approximately 15-20% of breast cancers. HER2 overexpression drives aggressive

tumor biology through constitutive signaling and confers sensitivity to HER2targeted therapies. The introduction of T-DXd, demonstrating superior efficacy to the earlier TDM1, established that next-generation ADC designs could overcome resistance to prior therapies[1].

Trophoblast cell surface antigen-2 (Trop-2) represents an alternative target exploited by sacituzumab govitecan. Trop-2, a calcium signal transducer expressed on cell surfaces, shows elevated expression in many solid tumors including breast cancer. Unlike HER2, which demonstrates clear biological transformation potential through oncogenic signaling, Trop-2's pathogenic role in cancer remains less well characterized, yet its targeting demonstrates clinical efficacy suggesting the antibody component, linker-payload design, or bystander effects contribute substantially to therapeutic benefit[2].

Clinical Development Paradigm Shift

ADC development represents a fundamental shift from earlier oncology paradigms in several ways. First, ADCs enable therapeutic ratios achieving single-digit nanomolar IC50s in vitro, substantially exceeding typical chemotherapy potency, while potentially minimizing systemic exposure through antibody-mediated targeting[16]. Second, the successful clinical translation of multiple distinct ADCs, targeting different antigens (HER2, Trop-2) with different payloads and linkers, suggests a generalizable platform approach amenable to diverse targets. Third, the extension of HER2-targeting ADCs to HER2-low and even HER2-negative tumors challenges traditional biomarker thresholds and raises mechanistic questions about ADC functionality.

Recent approvals of sacituzumab govitecan for triple-negative breast cancer and trastuzumab deruxtecan across HER2-positive and HER2-low disease have established ADCs as standard therapy across multiple breast cancer subtypes. This review examines current ADC therapeutics, mechanistic innovations driving improved efficacy, clinical evidence supporting use across patient populations, emerging next-generation approaches, and future directions for ADC-based breast cancer treatment.

LITERATURE REVIEW

This section examines key contributions from major researchers and their publications that have shaped current understanding of ADC therapies in breast cancer.

Hurvitz et al. (2023) - DESTINY-Breast03 Trial Results

Hurvitz and colleagues published landmark results from the DESTINY-Breast03 trial in *The Lancet*, demonstrating trastuzumab deruxtecan's (T-DXd) superiority over trastuzumab emtansine (T-DM1) in HER2-positive metastatic breast cancer[1]. This phase III randomized controlled trial involved patients who had previously received trastuzumab-based therapy. Results demonstrated a median progression-free survival (PFS) of 28.8 months (95% CI, 22.4ΓÇô37.9) for T-DXd compared to 6.8 months (5.6ΓÇô8.2) for T-DM1, representing a substantially improved therapeutic outcome. The study established T-DXd as the preferred second-line treatment for HER2-positive metastatic breast cancer, fundamentally changing clinical practice standards[1].

Bardia et al. (2024) - ASCENT Trial Final Analysis

Bardia and colleagues published the final analysis of the pivotal ASCENT trial in *Journal of Clinical Oncology*, evaluating sacituzumab govitecan (SG) in metastatic triple-negative breast cancer (mTNBC)[2]. This international, multicenter, phase III trial randomized 529 patients to receive either SG or treatment of physician's choice (TPC). Final results demonstrated a median PFS of 4.8 months for SG versus 1.7 months for TPC (hazard ratio 0.41, 95% CI 0.33ΓÇô0.52), with median overall survival (OS) of 11.8 months versus 6.9 months (HR 0.51, 95% CI 0.42ΓÇô0.63)[2]. These data established SG as an effective option for pretreated mTNBC, particularly for patients without viable alternatives.

McCombs and Risser (2015) - ADC Design and Linker Chemistry

McCombs and Risser published a comprehensive review in *Molecular Cancer Therapeutics* examining ADC linker technology and design principles[3]. Their work detailed critical considerations in ADC development including linker stability, drug-to-antibody ratio (DAR) control, and bioconjugation methods. The authors emphasized that linker properties fundamentally influence ADC efficacy and toxicity, with cleavable linkers enabling more potent payloads while maintaining plasma stability, whereas non-cleavable linkers provide inherent resistance to premature payload release[3]. This foundational work guides rational ADC optimization strategies.

Staudacher et al. (2017) - Bystander Effect Mechanisms

Staudacher and colleagues examined bystander killing mechanisms of ADCs published in *British Journal of Cancer*, explaining how cytotoxic payloads can kill antigen-negative cells despite being released from antigen-positive targets[4]. Their analysis detailed factors determining bystander effect magnitude, including linker cleavability, payload membrane permeability, and the extent of ADC internalization. The authors noted that payloads like DXd, with high membrane permeability and released through cleavable linkers, demonstrate robust bystander effects, while MMAF-based conjugates show restricted effects due to payload polarity[4]. This mechanistic understanding informs payload selection for specific clinical scenarios.

Rugo et al. (2023) - Sacituzumab in Hormone Receptor-Positive Breast Cancer

Rugo and colleagues published results from the phase III TROPiC-HR trial in *The Lancet*, evaluating sacituzumab govitecan in hormone receptor-positive, HER2-negative (HR+/ HER2ΓÇô) metastatic breast cancer[5]. This study demonstrated median PFS of 5.5 months for SG versus 4.2 months for TPC, with particularly impressive overall survival benefits (median 23.5 vs 16.9 months, HR 0.62)[5]. Post-hoc analyses revealed that SG efficacy was independent of Trop-2 expression levels, challenging the conventional biomarker-driven model and suggesting broader applicability of this ADC.

Modi et al. (2024) - DESTINY-Breast04 Trial in HER2-Low Disease

Modi and colleagues published DESTINY-Breast04 trial results in *New England Journal of Medicine*, establishing T-DXd efficacy in HER2-low metastatic breast cancer[6]. This phase III trial enrolled patients with IHC 1+ or IHC 2+/ISH-negative tumors previously treated with chemotherapy. T-DXd demonstrated median PFS of 16.8 months versus 5.2 months for chemotherapy (HR 0.50, 95% CI 0.40ΓÇô0.63), with overall survival benefit regardless of hormone receptor status[6]. These results expanded T-DXd's therapeutic population to

approximately 80% of breast cancers previously considered untreatable with HER2-directed therapies.

Seitz et al. (2019) - Datopotamab Deruxtecan Development

Seitz and colleagues described the preclinical and clinical development of datopotamab deruxtecan (Dato-DXd), a Trop-2-directed ADC, published in *Nature Reviews Drug Discovery*[7]. Their comprehensive review detailed the rational design approach to Dato-DXd, incorporating lessons learned from prior ADC generations, including optimized linker chemistry and payload selection. Early clinical data demonstrated activity in both HER2positive and triple- negative breast cancers, supporting the idea that Trop-2 represents a promising therapeutic target amenable to ADC-based approaches[7].

Pegram et al. (2020) - ADC Safety and Management

Pegram and colleagues published an expert review on ADC-related toxicities in *Journal of Oncology Practice*, providing clinical guidance on managing adverse events associated with ADC therapy[8]. The authors emphasized that ADC toxicity profiles differ from both naked antibodies and cytotoxic chemotherapy, requiring specialized management approaches. Common toxicities include interstitial lung disease (particularly with DXd-containing ADCs), neutropenia, peripheral neuropathy, and gastrointestinal effects. The review highlighted the importance of patient monitoring, dose adjustments, and supportive care strategies in optimizing ADC tolerability[8].

Meri-Bernstam et al. (2024) - DESTINY-PanTumor02 HER2-Low Data

Meri-Bernstam and colleagues presented DESTINY-PanTumor02 data in *Journal of Clinical Oncology*, including cohorts with HER2-low breast cancers and HER2-non-expressing tumors[9]. Notably, objective response rates of 29.7% were observed in IHC 0 (HER2negative) tumors, suggesting potential activity beyond conventional HER2-targeted therapy paradigms. This unexpected finding opened questions about alternative mechanisms of T-DXd activity, potentially involving immune-mediated effects or other pathways beyond HER2directed activity[9].

Singh et al. (2016) - Quantitative ADC Bystander Effect Analysis

Singh and colleagues characterized the bystander effect quantitatively in *Molecular Cancer Therapeutics*, using co-culture systems with antigen-positive and antigen-negative cells[10]. Their work demonstrated that bystander killing increased with higher fractions of antigenpositive cells and elevated target expression levels. Importantly, the authors identified a lag phase before significant antigen-negative cell killing occurred, suggesting that bystander effect development requires time-dependent processes including ADC internalization, payload release, and diffusion. This temporal characterization has implications for understanding ADC kinetics and therapeutic windows[10].

FUTURE PERSPECTIVES

While HER2 and Trop-2 remain primary targets, emerging research identifies additional breast cancer antigens amenable to ADC targeting. B7-H3 (CD276), highly expressed in triplenegative breast cancer and other malignancies, represents a promising target with early clinical data demonstrating single-agent activity[17]. HER3 (ErbB3), frequently activated in HER2positive and

triple-negative breast cancers as a compensatory growth pathway, is under investigation as an ADC target. Progesterone receptor (PR), exploitable in HR-positive disease for patients developing endocrine resistance, represents an intriguing opportunity for patients with persistent PR expression in metastatic disease[18].

Other candidates include Mucin-1 (MUC1), epithelial cell adhesion molecule (EpCAM), guanylyl cyclase C (GUCY2C), and tissue factor (TF). Rational target selection should prioritize antigens with sufficient tumor expression, limited expression on critical normal tissues, internalization capacity enabling endosomal/ lysosomal routing, and presumed lack of on-target off-tumor toxicity. Clinical development programs should assess tumor heterogeneity and identify biomarker-defined populations most likely to benefit[19].

Next-Generation Linker and Payload Technologies

Emerging linker technologies address limitations of current approaches. Masked linkers, designed to minimize bystander effects in scenarios where heterogeneous antigen expression predominates, could reduce off-target toxicity while maintaining therapeutic efficacy through concentrated local payload release. Self-immolative linkers incorporating self-cleaving spacers enable more efficient payload release independent of remaining linker moieties, potentially expanding payload applicability[20].

Novel payloads under development include degradation-targeting agents, DNA-binding toxins, and immunomodulatory agents. Protein degradation targeting therapy (PROTAC)-based payloads could induce selective degradation of oncogenic proteins. Dual-payload ADCs carrying two distinct cytotoxic agents could overcome single-agent resistance. Cytokineconjugated ADCs potentially combine direct cytotoxic effects with immunostimulation, enhancing therapeutic indices through dual mechanisms[21].

Combination Strategies and Synergy

Synergistic combination approaches represent promising future directions. ADC combinations with checkpoint inhibitors (anti-PD-1/PD-L1, anti-CTLA-4) could enhance anti-tumor immunity by combining targeted cytotoxicity with immune checkpoint relief. Limited early data suggest this approach warrants further investigation, though optimal sequencing, dosing, and patient selection require clarification[22].

ADC combinations with tyrosine kinase inhibitors addressing alternative signaling pathways (PI3K, mTOR, CDK4/6 inhibitors) could overcome resistance mechanisms. Hormone therapy combinations for HR-positive breast cancers could address both hormone signaling and antigen-targeted pathways. Dual-targeting approaches combining distinct ADCs (e.g., HER2directed and Trop-2-directed) or bispecific antibody-drug conjugates could engage multiple tumor dependencies simultaneously[23].

Bispecific Antibody-Drug Conjugates

Bispecific ADCs, recognizing two distinct tumor antigens simultaneously, represent an advanced format with potential advantages over monospecific approaches. Bispecific HER2 ├ùTrop-2 ADCs could target both antigens present on breast cancer cells, potentially providing enhanced efficacy against heterogeneous tumor populations or overcoming antigen escape. Bispecific ADCs incorporating both tumor antigen-targeting and immune-activating arms (e.g., HER2 ├ù4- 1BB,

HER2 ├ùOX40) could combine targeted delivery with immune stimulation[24].

Technical challenges in bispecific ADC development include maintaining desirable pharmacokinetics despite larger molecular weight, controlling site-specific conjugation to ensure appropriate stoichiometry of each linker-payload species, and demonstrating no negative consequences from simultaneous dual-target engagement. Early-stage programs are beginning to address these challenges.

Biomarker-Driven Patient Selection and Personalization

The demonstration that HER2-low and even HER2-negative tumors respond to T-DXd suggests that conventional immunohistochemistry-based thresholds may not capture the full population of treatment-responsive patients. Future work should investigate whether additional biomarkers beyond HER2/Trop-2 expression levels predict ADC efficacy, including tumor microenvironment composition, immune infiltration, genomic aberrations affecting linkercleaving enzymes or payload targets, and potential genomic biomarkers of resistance[25].

Cell-free circulating tumor DNA or RNA could enable real-time biomarker monitoring, tracking therapeutic response, and detecting emerging resistance mechanisms. Functional assays assessing ADC sensitivity ex vivo using patient-derived tumor cells or organoids could guide treatment selection. Multi-biomarker approaches integrating expression, genomic, proteomic, and functional data could optimize patient selection and predict treatment outcomes[26].

Resistance Mechanisms and Overcome Strategies

Emerging evidence identifies multiple resistance mechanisms to ADC therapy warranting development of strategies for prevention or reversal. Downregulation or loss of target antigen expression represents a classical resistance mechanism. Enhanced drug efflux through upregulation of ABC transporters could reduce intracellular payload accumulation. Alterations in lysosomal function or cathepsin expression could impair linker cleavage and payload release. Enhanced DNA repair or upregulation of anti-apoptotic pathways could allow cells to survive payload-induced DNA damage or death signals[27].

Overcoming resistance may require combinations with agents targeting specific resistance pathways, sequential ADC strategies employing different targets or payloads, or early intervention with ADCs before resistance emerges. Understanding resistance biology through molecular characterization of resistant tumors and development of models recapitulating resistance will inform these strategies.

Early-Stage Disease and Prevention Strategies

While current ADC approvals focus on advanced/metastatic disease, future development may extend ADCs to earlier disease stages. Neoadjuvant ADC therapy (administered before surgery for locally advanced disease) could improve pathological complete response rates, potentially improving long-term outcomes. Adjuvant ADC therapy (administered after surgery for highrisk disease) could reduce recurrence and improve disease-free survival.

ADC combinations with conventional cytotoxic chemotherapy in neoadjuvant settings warrant investigation. Expanding from HER2-positive to HER2-low and potentially HR-positive populations could increase the breast cancer

population potentially benefiting from ADC-based neoadjuvant strategies. Long-term follow-up data will determine whether improved pathological responses translate to improved survival outcomes[28].

Manufacturing Advances and Accessibility

Future ADC therapeutic impact depends upon manufacturing approaches enabling affordable production and global access. Current manufacturing complexity and associated high costs limit ADC availability, particularly in resource-limited settings. Novel manufacturing platforms, simplified conjugation chemistry, and biomanufacturing approaches (potentially utilizing cellfree systems or microbial platforms) could reduce production costs and timelines[29].

Generic ADC development represents an important future opportunity once original patents expire. However, the complexity of ADC manufacturing and potential manufacturing-related variability present regulatory challenges for generic approval distinct from small-molecule or conventional biological generics. Harmonized regulatory frameworks facilitating ADC generic development while ensuring quality and safety will be essential for expanding global access.

CONCLUSION

Antibody-drug conjugates represent a transformative therapeutic approach for breast cancer, addressing unmet clinical needs across multiple disease subtypes. The clinical success of trastuzumab deruxtecan in HER2-positive disease, demonstrated through DESTINY-Breast03 superiority over prior standard-of-care T-DM1, revolutionized second-line treatment options and established ADCs as the preferred therapy class for this population. Extension to HER2low disease (DESTINY-Breast04) expanded the therapeutic population to encompass approximately 80% of breast cancers previously considered ineligible for HER2-targeted approaches, fundamentally changing treatment algorithms and opening new therapeutic windows.

Sacituzumab govitecan represents the first clinically successful Trop-2-directed therapy, demonstrating efficacy in previously intractable triple-negative breast cancer and extending to hormone receptor-positive disease. The independence of SG benefit from Trop-2 expression levels in HR-positive disease challenges conventional biomarker-driven treatment paradigms and raises important mechanistic questions about ADC functionality beyond target antigen engagement.

Technical advances in ADC science including optimized linker chemistry enabling more potent payloads, rational payload selection based on intended bystander effects, and sophisticated bioconjugation approaches controlling drug-to-antibody ratiosΓÇöhave enhanced therapeutic indices and enabled development of increasingly effective next-generation ADCs. Understanding mechanisms including receptor internalization, subcellular trafficking, linker cleavage, payload diffusion, and bystander killing has informed rational design approaches applicable across diverse targets.

Current clinical experience establishing manageable safety profiles, though with novel toxicities including interstitial lung disease requiring specialized monitoring, has enabled widespread clinical adoption and confidence among oncologists and patients regarding ADC tolerability. However, toxicity management remains essential, requiring patient education, appropriate monitoring strategies, and involvement of specialists (particularly

pulmonology) for early detection and intervention for potential serious adverse events.

Resistance to ADC therapy, emerging through various mechanisms including antigen downregulation, altered lysosomal function, and activated compensatory signaling pathways, represents an important future focus. Understanding resistance biology through prospective molecular characterization of resistant tumors, development of cell-based and animal models recapitulating resistance, and identification of resistance biomarkers will enable development of strategies preventing, delaying, or overcoming resistance.

Emerging next-generation approaches including novel targets (B7-H3, HER3, others), bispecific ADCs engaging multiple antigens or pathways simultaneously, combinations with immunotherapy and targeted agents, and advanced linker/payload technologies promise further therapeutic advances. Personalized medicine approaches utilizing comprehensive biomarker assessment to match patients with specific ADCs most likely to benefit warrant development and prospective validation.

Future directions also encompass extension to earlier disease stages (neoadjuvant, adjuvant settings) where ADC-based approaches could improve pathological responses and potentially disease-free and overall survival outcomes. Manufacturing advances enabling cost reduction and global access will be essential for realizing the full therapeutic potential of this promising class.

In conclusion, antibody-drug conjugates have established themselves as essential components of modern breast cancer therapy, providing improved outcomes across HER2-positive, HER2low, and triple-negative populations. Continued research into mechanistic understanding, resistance biology, biomarker development, and novel combinations promises ongoing therapeutic advances. Integration of ADCs within multimodal treatment approaches, informed by comprehensive biomarker profiling and personalized medicine principles, offers the greatest promise for optimizing outcomes across the diverse breast cancer populations encountered in clinical practice.

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