

THE EVOLUTION OF ANTI-BODY DRUG CONJUGATES IN THE TREATMENT OF BREAST CANCER

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1 INTRODUCTION

Breast cancer is one of the most prevalent and challenging neoplasms worldwide. The search for more effective and less toxic therapies remains a priority in oncology. In this context, antibody drug conjugates (ADCs) have emerged as a revolutionary therapeutic class. ADCs combine the specificity of a monoclonal antibody with the cytotoxic potency of a chemotherapeutic agent. Their design aims to selectively eliminate tumor cells while sparing healthy tissues (NEWMAN et al., 2026). The evolution of ADCs has significantly changed breast cancer treatment. ADCs now offer more options for various disease subtypes, including those resistant to standard chemotherapy (SABIT et al., 2025; NEWMAN et al., 2026). This extended abstract explores the evolution of ADCs in breast cancer treatment. It addresses mechanisms of action, main approved and developing agents, current challenges, and future perspectives.

2 LITERATURE REVIEW

Antibody–drug conjugates (ADCs) are targeted therapeutics composed of a monoclonal antibody conjugated to a potent cytotoxic payload through a specialized chemical linker. This design allows for the selective delivery of cytotoxic agents to antigen expressing tumor cells, improving therapeutic efficacy and reducing off-target toxicity.

2.1 COMPONENTS OF ADCs

A Monoclonal Antibody is typically a humanized or fully human immunoglobulin G engineered to recognize a tumor-associated antigen with specificity. This selective antigen recognition enables preferential delivery of the cytotoxic payload to malignant cells while minimizing exposure to normal tissues (NEWMAN et al., 2026).

The linker is a chemical moiety that covalently connects the antibody to the cytotoxic payload. Linkers are generally classified as cleavable or non-cleavable. Cleavable linkers are designed to release the payload in response to specific intracellular or tumor-associated conditions, such as acidic pH, lysosomal proteases, or reducing environments. In contrast, non-cleavable linkers require complete proteolytic degradation of the antibody component within lysosomes to release the active cytotoxic

metabolite. The choice of linker significantly influences ADC stability, pharmacokinetics, therapeutic efficacy, and safety profile (NEWMAN et al., 2026).

Cytotoxic Payload is a potent antineoplastic agent that would generally exhibit an unacceptable therapeutic index if administered systemically as a free drug. Common payload classes include microtubule inhibitors, such as monomethyl auristatin E (MMAE) and DM1, as well as topoisomerase I inhibitors, such as DXd and SN-38 derivatives. Owing to their subnanomolar cytotoxic activity, these agents can induce tumor cell death even when delivered at relatively low intracellular concentrations (NEWMAN et al., 2026).

2.2 MECHANISM OF ACTION

Following antigen recognition, the ADC binds to the target cell surface and undergoes receptor-mediated endocytosis. The internalized ADC is subsequently trafficked to endosomal and lysosomal compartments, where the linker is cleaved or the antibody-linker complex is proteolytically degraded, depending on the linker design. This process releases the active cytotoxic payload, which interacts with its intracellular target and ultimately induces tumor cell death.

Certain ADCs can also exert a bystander effect, whereby membrane-permeable payload molecules diffuse into adjacent cells, including those expressing low or heterogeneous levels of the target antigen. This phenomenon may enhance antitumor activity in heterogeneous tumors but can also contribute to toxicity in surrounding tissues (SABIT et al., 2025). In addition, ADCs containing an intact Fc domain may retain immune effector functions, including antibody-dependent cellular cytotoxicity (ADCC), further contributing to their antitumor activity (NEWMAN et al., 2026).

2.3 EVALUATION OF ANTIBODY DRUG CONJUGATES

The clinical development of ADCs has evolved substantially since the introduction of gemtuzumab ozogamicin, the first ADC approved for the treatment of acute myeloid leukemia in 2000. Advances in antibody engineering, linker chemistry, payload design, and conjugation technologies have progressively improved therapeutic efficacy and safety.

A major milestone in breast cancer therapy was the approval of trastuzumab emtansine (T-DM1) in 2013, which demonstrated the clinical feasibility of targeted cytotoxic delivery in HER2-positive disease. More recently, next-generation ADCs such as trastuzumab deruxtecan (T-DXd) and sacituzumab govitecan (SG) have shown superior efficacy in several clinical settings, partly owing to higher drug-to-antibody ratios, optimized linker technologies, and enhanced bystander activity. Current research efforts are focused on the identification of novel tumor-associated antigens, the development of bispecific ADCs, site-specific conjugation strategies, and the incorporation of innovative payloads, including radiotherapeutic and immune-modulating agents (SPRING et al., 2021).

3 METHODOLOGY

This expanded abstract was developed based on a comprehensive review of the scientific literature published between 2021 and 2026. The literature search was conducted using Google Scholar and complemented by the examination of peer-reviewed scientific journals, with a focus on review articles, clinical trials, observational studies addressing recent advances in antibody drug conjugates (ADCs) for the treatment of breast cancer. The search strategy included the following keywords and descriptors: "Antibody Drug Conjugates breast cancer", "ADCs breast cancer evolution", "Trastuzumab deruxtecan", "Sacituzumab govitecan", "Datopotamab deruxtecan", and "HER2-low breast cancer". Publications were selected based on their relevance and the extent to which they provided detailed information regarding ADC mechanisms of action, clinical efficacy across different breast cancer subtypes, safety profiles, therapeutic limitations, current challenges, and future perspectives. The retrieved data were critically analyzed, synthesized, and organized according to the predefined topics addressed in this expanded abstract.

4 RESULTS AND DISCUSSION

The therapeutic scenario of breast cancer has been profoundly transformed by the development and clinical implementation of antibody–drug conjugates (ADCs). Several ADCs have received regulatory approval and have demonstrated substantial clinical benefit across distinct breast cancer subtypes.

4.1 APPROVED AND CLINICALLY RELEVANT ADCs

Trastuzumab Emtansine (T-DM1) was the first ADC approved for the treatment of breast cancer. It combines the anti-HER2 monoclonal antibody trastuzumab with the microtubule inhibitor DM1 through a non-cleavable linker. Clinical studies demonstrated superior efficacy in patients with HER2-positive metastatic breast cancer previously treated with trastuzumab and taxane-based therapies. Furthermore, T-DM1 received approval in the adjuvant setting after clinical trials showed a significant reduction in the risk of disease recurrence (SALVESTRINI et al., 2023).

Trastuzumab Deruxtecan (T-DXd) represents a major advance in HER2-directed therapy. This ADC consists of trastuzumab linked to deruxtecan, a potent topoisomerase I inhibitor. T-DXd has demonstrated noticeable antitumor activity across the HER2 expression spectrum, including HER2-positive, HER2-low, and HER2-ultralow tumors, thereby expanding treatment opportunities for a broader patient population. The DESTINY-Breast03 trial established the superiority of T-DXd over T-DM1, with significant improvements in both progression-free survival and overall survival among patients with HER2-positive metastatic breast cancer (CORTÉS et al., 2022).

Sacituzumab Govitecan (SG) is a TROP2-directed ADC that delivers SN-38, the active metabolite of irinotecan. Initially developed for triple-negative breast cancer (TNBC), in which TROP2 expression is highly prevalent, SG has demonstrated clinical efficacy regardless of TROP2 expression levels. The TROPiCS-02 trial reported significant improvements in progression-free survival and overall survival in heavily pretreated patients with HR-positive/HER2-negative metastatic breast cancer.

Additionally, SG has shown clinically meaningful intracranial activity, showing its potential benefit in patients with brain metastases (SPRING et al., 2021).

Datopotamab Deruxtecan (Dato-DXd) is one of the most recently approved ADCs for patients with unresectable or metastatic HR-positive/HER2-negative breast cancer. In the TROPION-Breast01 trial, Dato-DXd significantly improved progression-free survival compared with physician's choice chemotherapy. Importantly, although interstitial lung disease (ILD) remains a safety concern for deruxtecan-based ADCs, the incidence observed with Dato-DXd appears comparatively lower than that reported with T-DXd (OKAJIMA et al., 2021).

4.2 CHALLENGES AND FUTURE PERSPECTIVES

Despite the remarkable advances achieved with ADCs, several challenges remain. The identification of robust predictive biomarkers and the elucidation of mechanisms underlying primary and acquired resistance are critical areas of ongoing research (NEWMAN et al., 2026). Resistance to ADC therapy ultimately develops in a substantial proportion of patients, limiting the long-term clinical benefit of these agents. Moreover, defining the optimal sequencing of ADCs within the therapeutic algorithm of metastatic breast cancer remains an important unresolved issue (SABIT et al., 2025).

Future developments are expected to focus on next-generation ADC platforms, including bispecific targeting constructs, immunostimulatory antibody conjugates, and novel cytotoxic payloads with enhanced efficacy and safety profiles. The integration of biomarker-driven patient selection, a deeper understanding of resistance mechanisms, and the optimization of sequencing and combination strategies will be essential to fully realize the therapeutic potential of ADCs in breast cancer management (NEWMAN et al., 2026).

5 CONCLUSION

Antibody-drug conjugates (ADCs) have emerged as a major therapeutic advancement in breast cancer treatment, enabling the selective delivery of highly potent cytotoxic agents to tumor cells while reducing systemic exposure. The clinical development of ADCs, from trastuzumab emtansine (T-DM1) to next-generation agents such as trastuzumab deruxtecan (T-DXd), sacituzumab govitecan (SG), and datopotamab deruxtecan (Dato-DXd), has significantly expanded treatment options across multiple breast cancer subtypes and disease settings. Clinical evidence has demonstrated substantial improvements in efficacy outcomes, including progression-free survival and, in some cases, overall survival, while maintaining manageable safety profiles. Nevertheless, important challenges remain, especially regarding the emergence of resistance mechanisms, optimization of treatment sequencing and management of treatment-related adverse events. Ongoing research focused on the identification of novel molecular targets, innovative linker technologies, and next-generation payloads is expected to further enhance the therapeutic potential of ADCs. Collectively, these advances reinforce the central role of ADCs in the evolving scenario of precision oncology for breast cancer.

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