

# Research Progress and Challenges in the Use of TROP2-Targeted Antibody-Drug Conjugates for the Treatment of Triple-Negative Breast Cancer

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**Abstract:** Triple-negative breast cancer (TNBC), characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER-2) expression, has long been associated with limited treatment targets, a high risk of recurrence and metastasis, and a poor prognosis. In recent years, antibody-drug conjugates (ADCs), which link targeted antibodies to cytotoxic payloads, have provided a new avenue for breakthroughs in precision therapy for TNBC. TROP2 is highly expressed in various epithelial tumors and is associated with tumor invasion, metastasis, and poor prognosis; it has thus become a key target for TNBC-ADC drug development. Existing studies indicate that TROP2-ADCs, represented by Sacituzumab Govitecan (SG), can improve treatment outcomes for patients with advanced TNBC; however, challenges remain, including unclear mechanisms of resistance, a lack of biomarkers, difficulties in managing adverse reactions, and insufficient evidence for specific patient populations. Future efforts should focus on further optimizing ADC structures, refining TROP2 detection standards, and exploring personalized combination therapy strategies to advance the development of precision medicine for TNBC. This article provides a review of the fundamental mechanisms, clinical research progress, challenges in clinical application, and future directions for TROP2-ADC drugs in the treatment of TNBC.

**Keywords:** Triple-negative Breast Cancer; TROP2; Antibody-drug Conjugates; Mechanisms of Resistance.

## 1. Introduction

Breast cancer (BC) is a heterogeneous disease comprising a variety of tumors with different morphological, biological, and clinical phenotypes; among these, triple-negative breast cancer (TNBC)—which is negative for ER, PR, and HER2 expression—is considered one of the most aggressive subtypes [1–4]. In the past, due to the lack of ER, PR, and HER2 expression, treatment for TNBC has long relied primarily on chemoradiation, and overall treatment options have been relatively limited. In particular, there remains a significant unmet clinical need for treatment in early-stage, recurrent, or metastatic disease [1,5]. Although new strategies such as immunotherapy and PARP inhibitors have gradually been incorporated into the TNBC treatment regimen in recent years, the use of these precision medicines is limited to a small number of patients with specific biomarkers; therefore, research and development of targeted emerging therapies and effective targeted drugs are urgently needed for the clinical treatment of TNBC [1,5,6].

TROP2 is a transmembrane glycoprotein that is abnormally overexpressed in various epithelial-derived malignancies and is associated with tumor cell proliferation, invasion, migration, and poor prognosis [7–10]. Given that TROP2 is highly expressed in TNBC but relatively low in other normal tissues, and that it serves as a target for antibody recognition and drug delivery, it has gradually become an important focus in ADC drug R&D [8,11–13]. TROP2-ADCs recognize TROP2 on the surface of tumor cells via antibodies, deliver cytotoxic payloads into the tumor cells, and may produce a certain bystander effect, thereby enhancing antitumor activity [13–15].

This article will employ literature review and comparative analysis methods to present a review organized around four

aspects: First, to summarize the progress in basic research on TNBC, TROP2, and TROP2-ADC drugs; Second, summarizing the current status of clinical research on TROP2-ADCs for the treatment of TNBC; Third, analyzing the core challenges facing this class of drugs in terms of drug resistance, adverse reactions, biomarkers, and clinical application; And fourth, exploring future directions for drug structure optimization, early-stage treatment strategies, and combination therapies. This paper aims to provide a reference for subsequent TROP2-ADC-related research and the optimization of precision treatment strategies for TNBC.

## 2. Advances in Basic Research on TNBC, TROP2, and TROP2-ADC Drugs

### 2.1. Pathological Characteristics of TNBC and Limitations of Conventional Treatments

TNBC is typically defined as a subtype of breast cancer that is ER-negative, PR-negative, and HER2-negative. Compared with HR-positive or HER2-positive breast cancer, TNBC is more frequently associated with higher histological grade, greater proliferative activity, and a higher risk of recurrence and metastasis [1–5]. Due to the lack of clear, classic receptor targets for sustainable intervention, long-term chemotherapy and radiation therapy form the cornerstone of TNBC treatment. Drugs such as taxanes, anthracyclines, and platinum-based agents play a crucial role in adjuvant and advanced-stage therapy; however, their efficacy is influenced and limited by tumor heterogeneity, the development of drug resistance, and adverse effects [1,5].

More recently, immune checkpoint inhibitors and PARP inhibitors have created new treatment opportunities for selected patients. For example, patients with PD-L1-positive

tumors may benefit from immunotherapy, whereas those carrying BRCA1/2 mutations may respond to PARP inhibition [1,5,6]. Even so, these strategies do not apply to all patients with TNBC. This limitation has encouraged the exploration of therapeutic approaches with broader applicability. ADCs have emerged in this context as a promising strategy because they combine the antigen specificity of monoclonal antibodies with the potent cytotoxicity of chemotherapy. In principle, this design may reduce the nonselective nature of conventional chemotherapy while maintaining strong antitumor activity

## 2.2. Biological Functions of TROP2 and the Basis for Its Use as a Therapeutic Target

TROP2 is a transmembrane glycoprotein encoded by the TACSTD2 gene. It acts as an intracellular calcium signal transducer and is extensively involved in cell proliferation, adhesion, migration, and signal transduction processes [7,8]. In normal tissues, TROP2 is present on the surface of a small proportion of epithelial cells; however, its expression levels are abnormally elevated in various solid tumors, including breast, lung, gastric, and pancreatic cancers [7,9,10]. Previous studies have shown that high TROP2 expression may be associated with increased tumor aggressiveness, distant metastasis, and poor prognosis [9–12].

For TNBC, TROP2 holds significant value as a therapeutic target: First, TROP2 is highly expressed in a substantial proportion of TNBC tissues, providing a surface recognition basis for drug delivery [10–13]. Second, TROP2 is a transmembrane protein suitable for antibody binding and the induction of endocytosis, allowing the cytotoxic payload of ADCs to enter tumor cells [13, 15]. Third, the cytotoxic payload carried by some TROP2-ADCs can affect neighboring tumor cells via the bystander effect, which is of potential significance for tumor tissues with heterogeneous TROP2 expression [13, 14].

However, it should be noted that TROP2 is not a tumor-specific antigen; it is also expressed in some normal epithelial tissues. Therefore, how to reduce toxicity to normal tissues while ensuring antitumor activity is a critical issue that must be addressed in the design and clinical application of TROP2-ADCs [7,8,15].

## 2.3. Structural Composition and Mechanism of Action of TROP2-ADC Drugs

ADCs generally consist of three components: a targeting antibody, a linker, and a cytotoxic payload. The antibody determines antigen recognition on the tumor cell surface. The linker influences stability in circulation and the efficiency of payload release after cellular uptake. The payload determines the intensity and mechanism of cytotoxicity [15,16]. After administration, a TROP2-directed ADC binds to TROP2 on the tumor cell membrane. The antigen–ADC complex is then internalized, and the linker is cleaved or degraded in the intracellular environment. This process releases the cytotoxic payload, which may induce DNA damage, cell-cycle arrest, and ultimately tumor cell death [13,15,16].

Sacituzumab Govitecan is a representative TROP2-directed ADC. It links an anti-TROP2 antibody with a topoisomerase I inhibitor payload [17,18]. Topoisomerase I inhibitors interfere with DNA replication, leading to DNA damage and tumor cell death. Because this class of payload is highly cytotoxic, some released drug molecules can diffuse into adjacent tumor cells and generate a bystander effect [17–19]. This mechanism may help overcome intratumoral heterogeneity in TROP2 expression. At the same time, it may also contribute to adverse events such as myelosuppression and gastrointestinal toxicity [17,19].

In addition to SG, several newer TROP2-directed ADCs have attracted attention, including Datopotamab Deruxtecan (Dato-DXd) and Sacituzumab Tirumotecan (SAC-TMT). These agents differ in antibody design, linker stability, payload type, drug-to-antibody ratio (DAR), and payload release profile. Such structural differences may affect efficacy, safety, and patterns of resistance [15,16,20,21]. Therefore, comparing their molecular features and clinical performance is important for clarifying the therapeutic positioning of this drug class.

## 3. Clinical Progress of TROP2-Directed ADCs in TNBC

### 3.1. Clinical Development of Sacituzumab Govitecan

#### ANTIBODY-DRUG CONJUGATE (ADC) STRUCTURE & MECHANISM

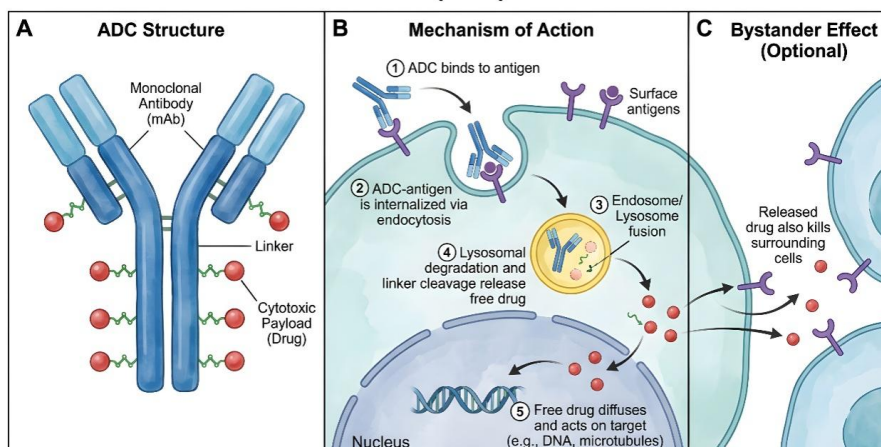


**Figure 1.** Antibody-drug conjugate structure and mechanism

Sacituzumab Govitecan is currently one of the most extensively studied TROP2-directed ADCs in TNBC. Most clinical evidence has been generated in patients with

unresectable locally advanced or metastatic TNBC who had previously received multiple lines of therapy. In the ASCENT study, SG significantly improved progression-free survival

(PFS) and overall survival (OS) compared with single-agent chemotherapy. It also increased the objective response rate (ORR) in patients with metastatic TNBC [17]. These findings indicate that TROP2-directed ADC therapy can provide meaningful clinical benefit for patients whose disease has limited response to conventional later-line chemotherapy.

The importance of SG extends beyond its role as a later-line treatment option. Its clinical success also validates TROP2 as a feasible therapeutic target in TNBC. Compared with conventional chemotherapy, ADCs use antibody-mediated targeting to increase the relative accumulation of cytotoxic payloads at tumor sites, reflecting a more precise therapeutic strategy [15,16]. Nevertheless, not all patients derive the same degree of benefit from SG. Some patients show primary resistance, whereas others experience only transient disease control before progression. These observations suggest that TROP2 expression, intratumoral heterogeneity, internalization efficiency, and intracellular resistance mechanisms may all influence treatment response [13,16,22].

### **3.2. Other TROP2-Directed ADCs and Ongoing Clinical Studies**

Several TROP2-directed ADCs other than SG are currently under clinical investigation. Datopotamab deruxtecan uses a TROP2-targeting antibody linked to a deruxtecan-based topoisomerase I inhibitor payload through a stable cleavable linker. Its linker and payload design differ from those of SG [20]. Early clinical studies have shown antitumor activity in advanced breast cancer. However, its comparative efficacy, safety profile, and optimal placement within the TNBC treatment sequence remain to be defined in larger studies [20,23].

Sacituzumab tirumotecan has also gained increasing attention. A key distinction between SAC-TMT and other TROP2-directed ADCs lies in its novel linker, which improves stability in circulation and may help reduce off-target toxicity [21]. Existing studies and reviews have noted that gastrointestinal toxicity, particularly diarrhea, is common with SG, whereas SAC-TMT may have a different toxicity spectrum. Even so, SAC-TMT can still cause off-tumor toxicities, including oral mucositis and stomatitis, which require further monitoring and management in subsequent clinical trials [21,23].

Although these agents have shown potential survival advantages over chemotherapy in TNBC, much of the current evidence remains preliminary or is concentrated in advanced-stage disease. It is therefore inappropriate to directly extrapolate these results to early TNBC. More randomized controlled trials are needed to determine whether TROP2-directed ADCs can improve survival outcomes and maintain acceptable safety in earlier treatment settings [19-23].

### **3.3. Efficacy and Safety Characteristics of TROP2-Directed ADCs**

The efficacy of TROP2-directed ADCs is commonly evaluated using ORR, PFS, and OS. Available evidence generally supports their potential superiority over conventional single-agent chemotherapy in recurrent or metastatic TNBC, particularly among patients who have previously failed standard treatments [17,19,20]. However, direct ranking of different TROP2-directed ADCs should be avoided. Existing trials differ in patient populations, prior treatment exposure, endpoint definitions, and follow-up

duration, making cross-trial comparisons unreliable.

In terms of safety, common adverse events associated with TROP2-directed ADCs include neutropenia, anemia, nausea, vomiting, diarrhea, fatigue, and alopecia [17,20,21]. For SG, toxicities related to its SN-38 payload make myelosuppression and gastrointestinal reactions major concerns in clinical management [17,19]. Different payload platforms may also produce distinct toxicity profiles. For example, some deruxtecan-based ADCs require careful monitoring for interstitial lung disease or pneumonitis [20,23]. Since many patients with TNBC have already received multiple lines of chemotherapy before ADC treatment, their bone marrow reserve, hepatic and renal function, and overall performance status may vary considerably. Individualized dose adjustment and close toxicity surveillance are therefore essential.

## **4. Key Challenges Facing the Clinical Application of TROP2-ADCs**

### **4.1. The Mechanisms of Primary and Secondary Resistance Have Not Yet Been Fully Elucidated**

Resistance remains a major obstacle to the durable efficacy of TROP2-directed ADCs and may arise at multiple stages of ADC action. Reduced or heterogeneous TROP2 expression limits ADC binding and uptake, whereas defective endocytosis, endosomal-lysosomal trafficking, or linker cleavage can reduce intracellular payload release [13,15,16,24]. Direct evidence comes from an SG-resistant TNBC case in which distinct metastatic lesions acquired either a TACSTD2 T256R mutation, which impaired TROP2 membrane localization and ADC internalization, or a TOP1 E418K mutation, which reduced sensitivity to the SN-38 payload. Functional cell models confirmed that these alterations caused antigen- and payload-level resistance, respectively [25]. Resistance to topoisomerase I inhibitor payloads may also involve TOP1 downregulation, enhanced DNA-damage repair, loss of the replication-stress regulator SLFN11, or increased drug efflux through ABCB1/ABCG2 transporters [16,18,24]. However, several of these mechanisms are derived from broader ADC or topoisomerase I inhibitor models and require further validation in TROP2-ADC-resistant TNBC models.

TNBC heterogeneity facilitates the selection of resistant subclones with altered TROP2 expression, intracellular processing, DNA-repair capacity, or payload sensitivity [1,4,13]. Although the bystander effect may eliminate neighboring TROP2-low cells, it cannot fully overcome complete antigen loss, poor tumor penetration, drug efflux, or payload-class resistance. Potential strategies should therefore be mechanism based: TROP2 loss may require alternative-antigen or bispecific ADCs, whereas preserved TROP2 with TOP1-pathway resistance may be addressed using ADCs carrying different payload classes or combinations with PARP, ATR, or WEE1 inhibitors. Linker optimization and efflux-resistant payloads may further improve intracellular drug exposure [14,19,23,24]. Serial biopsies or circulating tumor DNA monitoring could help distinguish antigen-level from payload-level resistance and guide subsequent treatment selection.

## **4.2. Management of Adverse Reactions Still Needs to Be Standardized**

Although TROP2-ADCs offer the advantage of targeted delivery, their antitumor effect essentially relies on a potent cytotoxic payload; therefore, adverse reactions are inevitable. For example, neutropenia increases the risk of infection, while symptoms such as diarrhea, nausea, and vomiting may affect patients' nutritional status and treatment adherence [17, 20, 21]. Furthermore, for patients with advanced TNBC who have previously undergone multiple lines of treatment, their baseline bone marrow reserve is compromised, and the occurrence of adverse reactions may lead to treatment delays, dose reductions, or even discontinuation [17,19].

Therefore, future clinical practice requires further standardization of strategies for monitoring, preventing, and managing TROP2-ADC-related adverse reactions, including routine blood tests, infection risk assessment, antiemetic and antidiarrheal treatments, dose adjustment guidelines, and early identification of specific toxicities.

## **4.3. Insufficient TROP2 Testing Standards and Predictive Biomarkers**

Although TROP2 is the central target of this ADC class, standardized methods for assessing TROP2 expression have not yet been fully established. Different studies may use different staining platforms, scoring systems, and positivity thresholds, which limits the comparability of TROP2 expression results. In addition, the relationship between TROP2 expression and response to TROP2-directed ADC therapy is not strictly linear. Clinical data indicate that some patients with high TROP2 expression do not achieve satisfactory responses, whereas some patients with moderate expression still benefit from treatment [13,17,23]. These findings suggest that TROP2 expression alone may be insufficient as a precise predictive biomarker.

ADC efficacy is influenced by multiple factors, including antigen expression, antigen internalization, linker stability, payload sensitivity, tumor microenvironment characteristics, and DNA damage repair capacity. Future biomarker development should therefore move beyond single-marker assessment and incorporate multidimensional predictive models. Such models may improve patient selection and help identify individuals most likely to benefit from TROP2-directed ADC therapy.

## **4.4. Limitations in Clinical Application and Insufficient Evidence for Specific Populations**

The clinical application of TROP2-ADCs also faces challenges related to accessibility, treatment sequencing, and insufficient evidence for specific populations. First, the high costs of ADC drug R&D and production may affect drug accessibility across different regions and healthcare systems [5,23]. Second, as immunotherapy, PARP inhibitors, platinum-based chemotherapy, and other ADC drugs are incorporated into the TNBC treatment regimen, further exploration is needed to determine the optimal timing for TROP2-ADC administration [1,5,23].

Regarding specific patient populations, the proportion of patients with brain or lung metastases, elderly patients, patients with hepatic or renal impairment, and those with multiple comorbidities has been limited in clinical trials, resulting in insufficient evidence for drug use in real-world

settings [17, 20, 23]. TNBC patients have a higher risk of brain and lung metastases, yet the effective exposure of large-molecule ADCs and their payloads across the blood-brain barrier requires further validation through research [1,23]. Therefore, future studies should prioritize such clinical research and subgroup analyses of special populations to enhance the reliability of clinical decision-making.

## **5. Future Directions for TROP2-ADCs**

### **5.1. Optimization of ADC Architecture and Generation of New Therapeutic Constructs**

Further refinement of ADC design is likely to remain one of the main routes for improving TROP2-targeted treatment. The antibody backbone is a key element in this process. Antibodies engineered to bind TROP2 with greater affinity and higher antigen specificity may strengthen tumor targeting and, at the same time, reduce unintended recognition of normal tissues that express TROP2 at lower levels. Linker chemistry also requires careful adjustment. An effective linker should remain intact during systemic circulation but permit adequate payload release once the ADC has entered tumor cells. Early cleavage in the bloodstream may expose normal tissues to the cytotoxic compound and increase systemic adverse effects. By contrast, a linker that is too resistant to cleavage may limit intracellular drug availability and weaken cytotoxic activity. Payload innovation is another important direction. Since many current TROP2-directed ADCs depend on topoisomerase I inhibition, cytotoxic agents with different mechanisms of action may provide a way to bypass or delay resistance to existing platforms. In addition, the drug-to-antibody ratio should be optimized within a suitable range. Low DAR values may fail to deliver enough cytotoxic payload, whereas excessive drug loading can reduce molecular stability and impair pharmacokinetic behavior [15,19,23].

Future ADC platforms may move beyond conventional single-antibody, single-payload designs. Possible approaches include bispecific antibody-based ADCs, payloads with immunoregulatory activity, and release systems that allow more precise control of drug liberation. These designs may increase antitumor efficacy while broadening the therapeutic window. Their practical value still needs to be confirmed through systematic preclinical work and subsequent clinical evaluation.

### **5.2. Movement into Early TNBC and Development of Patient-Specific Combination Strategies**

The most mature clinical data for TROP2-directed ADCs currently come from patients with advanced or metastatic TNBC who have received prior lines of therapy. Clinical investigation is now extending this class of agents into earlier stages of treatment. Trials are exploring their use in first-line metastatic settings as well as in perioperative therapy, including neoadjuvant and adjuvant approaches.

The phase III study conducted by Dent et al. illustrates this change in development strategy. In that trial, sacituzumab tirumotecan plus pembrolizumab is being assessed as adjuvant therapy for patients with early high-risk TNBC who have residual disease after neoadjuvant treatment and do not achieve pathological complete response [22]. This study

suggests that TROP2-directed ADCs may eventually be used not only in refractory metastatic disease but also in early high-risk TNBC, where the therapeutic aim is to reduce recurrence. It may also provide evidence on whether ADCs and immune checkpoint blockade can act cooperatively in this setting. If ongoing studies demonstrate clinical benefit, TROP2-targeted ADCs could become relevant across a broader continuum of TNBC care.

Combination treatment is another route by which therapeutic activity may be enhanced and resistance may be postponed. The pairing of TROP2-directed ADCs with immunotherapy is supported by mechanistic considerations. Tumor cell death induced by ADCs can increase antigen exposure and may alter the immune microenvironment, thereby creating conditions that favor checkpoint inhibitor activity [23,26]. Other combinations are also being considered. PARP inhibitors, platinum compounds, and radiotherapy may intensify DNA damage when used with ADCs, offering a potential basis for synergistic antitumor effects [6,18,23].

At the same time, combined regimens may produce more complicated toxicity profiles. Bone marrow suppression, gastrointestinal toxicity, and immune-related adverse events may overlap or amplify one another, making dose adjustment and supportive care more difficult. For this reason, future combination strategies should be guided by patient and tumor characteristics rather than by simple treatment intensification. Molecular features, previous treatment exposure, baseline organ function, and individual vulnerability to adverse events should all be incorporated into regimen selection.

### 5.3. Improving Standardized TROP2 Testing and Developing New Biomarkers

To promote the precise application of TROP2-ADCs, unified TROP2 testing standards must be established in the future, including but not limited to sample types, testing platforms, and scoring systems [10–12]. At the same time, composite biomarkers capable of predicting both efficacy and toxicity should be explored, rather than relying solely on single TROP2 expression levels. The efficacy of ADCs is influenced by factors such as antigen endocytosis efficiency, linker stability, payload sensitivity, the tumor microenvironment, DNA damage repair capacity, and immune status; therefore, this shortcoming can be addressed in the future by establishing a multidimensional predictive system.

Such a multidimensional system could include TROP2 expression, genetic mutation profiles, transcriptomic information, drug metabolism-related genes, dynamic changes in circulating tumor DNA, and imaging parameters [9, 11, 24, 27]. Only by establishing a standardized, reproducible, and clinically actionable biomarker system can we truly advance the personalized and precision application of TROP2-ADCs.

## 6. Conclusion

TROP2-ADCs represent one of the major advances in the treatment of triple-negative breast cancer (TNBC) in recent years. TROP2-ADCs, represented by SG, have demonstrated clinical value superior to traditional single-agent chemotherapy in advanced TNBC, proving the feasibility of TROP2-targeted treatment strategies. At the same time, research on novel TROP2-ADCs such as Dato-DXd and sac-

TMT is expanding the range of drug options and treatment stages in this field.

Despite these advances, several challenges remain. Future research should focus on ADC structural optimization, earlier-stage TNBC treatment, rational combination strategies, and standardized biomarker systems. With continued integration of basic mechanistic studies and clinical research, TROP2-directed ADCs may play an increasingly important role in precision therapy for TNBC and provide new opportunities to improve long-term patient outcomes.

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