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EDITORIAL

Advances in TROP2-targeted antibody-drug conjugates for breast cancer therapy: into the new era

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Breast cancer is a heterogeneous disease stratified by hormone receptors (HRs) and human epidermal growth factor receptor 2 (HER2) status and each subtype has divergent therapeutic needs. Despite the current therapeutic advances, resistance to standard therapies remains pervasive, underscoring the demand for novel strategies. Antibody-drug conjugates (ADCs) offer a powerful strategy by combining tumor-specific antibodies to potent cytotoxins, enabling selective delivery and minimizing off-target toxicity[1]. TROP2, a transmembrane glycoprotein broadly overexpressed in breast cancer, has emerged as a promising ADC target. The approval of datopotamab deruxtecan (Dato-DXd) with sacituzumab govitecan (SG) and the incorporation of these ADCs into the National Comprehensive Cancer Network (NCCN) guidelines (v2.2025) highlight the fast penetration of TROP2 ADCs into clinical practice[2]. This editorial provides timely insights into optimizing TROP2-targeted strategies to improve outcomes across breast cancer subtypes.

Significance of TROP2 in breast cancer

TROP2, which is encoded by the *TACSTD2* gene on chromosome 1p32, is overexpressed in multiple epithelial cancers, including breast cancer, where TROP2 has an essential role in tumor progression and metastasis[3]. Mechanistically, TROP2 activates key signaling pathways, such as the PI3K/AKT, MAPK/ERK, JAK/STAT, and β-catenin pathways, and facilitates epithelial-mesenchymal transition (EMT)[4]. Prognostically, TROP2 overexpression is strongly correlated with aggressive clinicopathologic features and poor prognosis in all subtypes. In triple-negative breast cancer (TNBC), high TROP2 levels predict poor prognosis in TNBC patients with reduced overall survival (OS), increased recurrence, and a more invasive phenotype. High TROP2 expression correlates with trastuzumab resistance in HER2+ tumors[5]. TROP2 overexpression has been linked to increased tumor proliferation and recurrence risk in HR+/HER2− disease, suggesting prognostic relevance even in less aggressive subtypes. Collectively, these findings establish TROP2 as a prognostic biomarker and a compelling therapeutic target across diverse breast cancer subtypes.

Structures of TROP2-targeted ADCs

TROP2-targeted ADCs are composed of an antibody, a linker, and a cytotoxic payload. The mechanism begins with the antibody binding to TROP2 on cancer cells following receptor-mediated endocytosis and acidic endosome- or lysosome-mediated linker cleavage, which releases the cytotoxic payload directly into the interior of the cell, enabling direct and localized cell killing and adjacent killing caused by the bystander effect[6].

Despite this shared mechanism, SG, Dato-DXd, and sacituzumab tirumotecan (Sac-TMT), the three most clinically advanced TROP2 ADCs, differ structurally, which shapes the pharmacologic properties (**Table 1**). SG employs a hydrolyzable linker to attach SN-38, the active metabolite of irinotecan, inducing DNA damage and apoptosis (IC_{50} = 2.78 μmol/L) but relatively unstable circulation behavior, which contributes to hematologic and gastrointestinal toxicities. Dato-DXd, the next-generation ADC, links a highly potent topoisomerase I inhibitor payload [DXd (IC_{50} = 0.31 μmol/L)] *via* a stable tetrapeptide cleavable linker. This design improves stability, enhances tumor-selective release, and supports strong bystander killing with fewer systemic toxicities. Sac-TMT couples TROP2 antibody with KL610023, a novel topoisomerase I inhibitor (IC_{50} = 0.7 μmol/L) *via* an optimized cleavable linker with moderate stability. Collectively, these structural distinctions underscore

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Table 1 Structure characteristics of anti-TROP2 ADCs

Features	Datopotamab Deruxtecan	Sacituzumab Govitecan	Sacituzumab Tirumotecan
Chemical name	Dato-DXd (DS-1062)	SG (IMMU-132/SG)	Sac-TMT (SKB-264)
Developing company	AZ & Daiichi Sankyo	Gilead	Colun Pharmaceutical
Ab	MAAP-9001a (humanized IgG1)	hRS7 (humanized IgG1)	hRS7 (humanized IgG1)
Ab affinity (KD)	0.74 nM	0.292 nM	0.312 nM
Payload	DXd (derivative of exatecan)	SN-38 (active metabolite of irinotecan)	KL610023 (derivative of belotecan)
Payload characteristics	IC_{50} = 0.31 μmol/L, short half-life (1 mg/kg of DXd T1/2 1.37 h)	IC_{50} = 2.78 μmol/L, long half-life (~15–20 h)	IC_{50} 0.7 μmol/L, half-life (0.24 mg/kg KL610023 T1/2 5.7 h)
Linker	GGFG linker	CL2A linker	CL2A-modified linker
Linker type	Enzymatically cleavable	pH-dependent	pH-dependent & enzymatically cleavable
Linker stability	High stability, 1.4–5.5% payload released in plasma after 21 d	Low stability, 100% payload released in plasma after 2 d	Medium stability, 70% payload released in plasma after 6 d
ADC intact drug half-life	NSCLC: 4.8 d in plasma	mTNBC: 23.4 h (~0.98 d) at 6 mg/kg dosing	Locally advanced/metastatic solid tumors: ~36 h (1.5 d)
Dosage regimen	6 mg/kg q3w	10 mg/kg, D1 & D8 q3w	5 mg/kg q2w
DAR	4:1	7.6:1	7.4:1
Bystander effect	Yes	Yes	Yes

ADC, antibody-drug conjugate; Ab, antibody; DAR, drug-to-antibody ratio; Dato-DXd, datopotamab deruxtecan; h, hours; IC_{50}, half maximal inhibitory concentration; KD, dissociation constant; mTNBC, metastatic triple-negative breast cancer; NSCLC, non-small cell lung cancer; q2w, every two weeks; q3w, every three weeks; SG, sacituzumab govitecan; T1/2, half-life.

the rapid evolution of TROP2 ADCs and the capacity to refine efficacy and safety profiles in breast cancer.

Clinical developments of TROP2 ADCs as monotherapy in breast cancer

Sacituzumab govitecan

SG was the first TROP2-targeted ADC to demonstrate meaningful clinical activity and receive global approval (**Figure 1**). Early evidence came from the phase I/II **IMMU-132-01 trial**, which included > 100 pre-treated metastatic triple-negative breast cancer (mTNBC) patients[7]. SG achieved an objective response rate (ORR) of 33.3%, a median duration of response (DOR) of 7.7 months, a median progression-free survival (mPFS) of 5.5 months, and a median OS (mOS) of 13.0 months, which established a proof-of-concept in this difficult-to-treat population (**Table 2**).

The pivotal **phase III ASCENT trial** confirmed SG efficacy. SG significantly outperformed physician's choice chemotherapy in 529 patients with refractory mTNBC: ORR, 31.0% *vs.* 4.0%; mPFS, 4.8 *vs.* 1.7 months (HR = 0.41); and mOS, 11.8 *vs.* 6.9 months (HR = 0.51). Adverse events (AEs) were manageable, with neutropenia, diarrhea, and anemia the most common grade ≥ 3 toxicities[8,9]. Eighty patients with refractory mTNBC achieved ORR 38.8% and mPFS 5.6 months in the **Chinese EVER-132-001 bridging study**, confirming the value of SG across populations. Furthermore, the **phase III ASCENT-03 trial** showed that SG significantly improved the mPFS [9.7 *vs.* 6.9 months (HR = 0.62)] in the first-line setting for mTNBC patients who were not candidates for immunotherapy when compared to chemotherapy, as reported at the 2025 European Society for Medical Oncology (ESMO) Congress; OS data were not mature.

The results of the pivotal **phase III TROPiCS-02 trial** showed that SG improved survival [mPFS: 5.5 *vs.* 4.0 months (HR = 0.66); mOS: 14.4 *vs.* 11.2 months (HR = 0.79)] of pre-treated patients with HR+/HER2− metastatic breast cancer (mBC) when compared to chemotherapy[10]. Consistent benefits of SG were also shown in the **phase III EVER-132-002** Asia bridging study. Building on its metastatic success, SG has been tested in earlier stages of disease. The **NeoSTAR trial** evaluated SG as neoadjuvant monotherapy in untreated early TNBC. Approximately two-thirds of patients responded

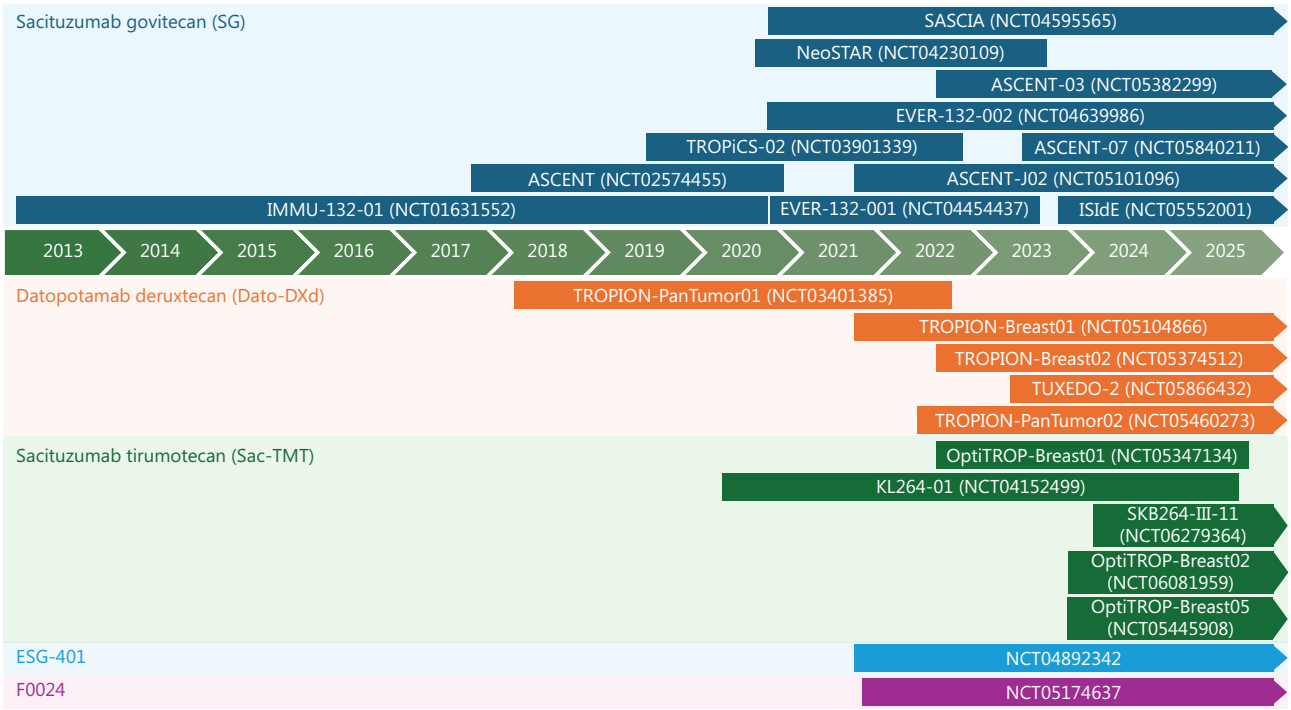


Figure 1 Clinical timeline of TROP2-targeted antibody-drug conjugates as monotherapy in breast cancer (2013–2025). Each bar represents the start and progression of pivotal clinical studies evaluating sacituzumab govitecan (SG), datopotamab deruxtecan (Dato-DXd), sacituzumab tirumotecan (Sac-TMT), ESG-401, and F0024 as monotherapy in breast cancer. Key ongoing and completed trials are annotated with corresponding NCT numbers.

radiographically with 30% achieving a pathologic complete response (pCR) without additional chemotherapy[11]. The ongoing **phase III SASCIA trial** is further assessing SG as adjuvant therapy in HER2-negative breast cancer with residual disease after neoadjuvant treatment.

Taken together, SG has become a benchmark therapy in mBC and validated across pivotal, bridging, and early-stage trials, making SG the most extensively studied TROP2 ADC to date.

Datopotamab deruxtecan

Following the food and drug administration (FDA) approval in 2025, Dato-DXd became the second TROP2-targeted ADC authorized for the treatment of unresectable or metastatic HR+/HER2− breast cancer. Early evidence came from the **phase I TROPION-PanTumor01 trial**, which showed favorable activity (ORR: 32% and 27%, respectively; mPFS: 4.4 and 8.3 months, respectively) and tolerable safety of Dato-DXd in both pretreated mTNBC and HR+/HER2− cohorts[12].

These findings were confirmed in phase III trials. The **TROPION-Breast01 trial** randomized pretreated HR+/HER2− mBC patients to Dato-DXd or chemotherapy. Dato-DXd significantly improved mPFS [6.9 *vs.* 4.9 months (HR = 0.63)] and ORR (36% *vs.* 23%; odds ratio: 1.95, 95% CI: 1.41–2.71) across almost all subgroups. OS was not statistically different at the interim analysis but sensitivity analyses suggested a trend toward benefit, especially in HER2 IHC 0 patients. Importantly, toxicity was generally favorable; specifically, grade ≥ 3 AEs occurred in 21% of patients treated with Dato-DXd *vs.* 45% of patients treated with chemotherapy and stomatitis, nausea, and fatigue were the main manageable side effects[13]. As reported at the 2025 ESMO Congress, the **TROPION- Breast02** trial showed that Dato-DXd significantly improved mPFS [10.8 *vs.* 5.6 months (HR = 0.57)] and mOS [23.7 *vs.* 18.7 months (HR = 0.79)] at the 27.5-month follow-up evaluation in the first-line setting of immunotherapy-ineligible mTNBC compared to chemotherapy. Higher ORR (62.5% *vs.* 29.3%) and longer DOR (12.3 *vs.* 7.1 months) were also noted in the Dato-DXd group, grade ≥3 AEs were comparable (33% *vs.* 29%), and fewer patients discontinued therapy due to toxicity (4% *vs.* 7%)[14].

Regional studies have confirmed the aforementioned results. Dato-DXd yielded an ORR of 39% and mPFS of 8.1 months with fewer grade ≥3 AEs than chemotherapy in the **China cohort of TROPION-Breast01** trial. The China **TROPION-PanTumor02** study resulted in an ORR of 34% and mOS of 13.5 months in patients with mTNBC.

Table 2 Clinical developments of TROP2 ADCs as monotherapy in breast cancer treatment

NCT number	Study name	Phase	Cancer status	Study population	Study design	Efficacy outcomes
Sacituzumab govitecan (SG)						
NCT01631552	IMMU-132-01	I/II	Advanced	mTNBC and HR+ mBC	SG	mTNBC: ORR 33.3%, mDOR 7.7 mo, mPFS 5.5 mo, mOS 13.0 mo, CBR 45.4%; HR+ mBC: ORR 31.5%, mDOR 8.7 mo, mPFS 5.5 mo, mOS 12.0 mo, CBR 44.4%
NCT02574455	ASCENT	III	Advanced	mTNBC	SG *vs.* TPC	mPFS 4.8 *vs.* 1.7 mo; mOS 11.8 *vs.* 6.9 mo; ORR 31.0% *vs.* 4.0%; mDOR 6.3 *vs.* 3.6 mo; mTTR 1.5 *vs.* 1.5 mo
NCT03901339	TROPiCS-02	III	Advanced	HR+/HER2− mBC	SG *vs.* TPC	mPFS 5.5 *vs.* 4 mo; mOS 14.4 *vs.* 11.2 mo; ORR 21.0% *vs.* 14.0%; mDOR 8.1 *vs.* 5.6 mo; CBR 34% *vs.* 22%
NCT04454437	EVER-132-001	II	Advanced	Chinese mTNBC	SG	ORR 38.8%; mDOR 11.6 mo; mPFS 5.6 mo; mOS 14.7 mo; CBR 46%
NCT04639986	EVER-132-002	III	Advanced	HR+/HER2− mBC	SG *vs.* TPC	mPFS 4.3 *vs.* 4.2 mo; mOS 21.0 *vs.* 15.3 mo; ORR 20.0% *vs.* 15.0%; mDOR 5.3 *vs.* 5.2 mo; CBR 38% *vs.* 22%
NCT05101096	ASCENT-J02	I/II	Advanced	Japanese mTNBC	SG	ORR 25%; mDOR 6.2 mo; mPFS 5.6 mo
NCT05382299	ASCENT-03	III	Advanced	mTNBC	SG *vs.* TPC	mPFS 9.7 *vs.* 6.9 mo; ORR 48.0% *vs.* 46.0%; mDOR 12.2 *vs.* 7.2 mo
NCT05552001	ISIdE	III	Advanced	2nd line mTNBC	SG	On going
NCT05840211	ASCENT-07	III	Advanced	HR+/HER2− mBC	SG *vs.* TPC	On going
NCT04647916	/	II	Advanced	HER2− mBC (brain metastases)	SG	On going
NCT04230109	NeoSTAR	II	Early-neoadjuvant	Neoadjuvant treatment in TNBC	SG	pCR 30%; ORR 64%; 2 year-EFS 95%
NCT04595565	SASCIA	III	Early-adjuvant	HER2− BC with residual disease after neoadjuvant chemotherapy	SG *vs.* TPC	On going
Datopotamab deruxtecan (Dato-DXd)						
NCT03401385	TROPION-PanTumor01	I	Advanced	mTNBC, HR+/HER2− mBC	Dato-DXd	mTNBC: ORR 31.8%, mDOR 16.8 mo, mPFS 4.4 mo, mOS 13.5 mo, CBR 38.6%; mTTR 1.36 mo HR+ mBC: ORR 26.8%, mPFS 8.3 mo, CBR 43.9%; mTTR 2.8 mo
NCT05104866	TROPION-Breast01	III	Advanced	HR+/HER2− mBC	Dato-DXd *vs.* TPC	mPFS 6.9 *vs.* 4.9 mo; mTFST 8.2 *vs.* 5 mo; ORR 36.4% *vs.* 22.9%; mDOR 6.7 *vs.* 5.7 mo; mTTR 2.7 *vs.* 2.6 mo

Table 2 Continued

NCT number	Study name	Phase	Cancer status	Study population	Study design	Efficacy outcomes
NCT05374512	TROPION-Breast02	III	Advanced	mTNBC	Dato-DXd *vs.* TPC	mPFS 10.8 *vs.* 5.6 mo; mOS 23.7 *vs.* 18.7 mo; ORR 62.5% *vs.* 29.3%; mDOR 12.3 *vs.* 7.1 mo
NCT05866432	TUXEDO-2	II	Advanced	mTNBC (brain metastases)	Dato-DXd	IC-ORR 37.5%
NCT05460273	TROPION-PanTumor02	I/II	Advanced	mTNBC (Chinese)	Dato-DXd	ORR 33.8%; DCR 72.7%; mDOR 6.7 mo; mPFS 5.3 mo; mOS 13.5 mo
NCT01042379	I-SPY2.2	II	Early-neoadjuvant	HER2− BC	Dato-DXd	HR+HER2−: pCR 9% HR−HER2−: pCR 29%
Sacituzumab tirumotecan (Sac-TMT)						
NCT04152499	KL264-01	I/II	Advanced	mTNBC HR+/HER2− mBC	Sac-TMT	mTNBC: ORR 37.3%; mDOR 11.5 mo; mPFS 5.7 mo; mOS 15.7 mo HR+/HER2− mBC: ORR 31.7%; mDOR 9.5 mo; mPFS 8.0 mo; mOS 13.9 mo
NCT05347134	OptiTROP-Breast01	III	Advanced	mTNBC	Sac-TMT *vs.* TPC	mPFS 6.7 *vs.* 2.5 mo; ORR 45.4% *vs.* 12.0%; mDOR 7.1 *vs.* 3.0 mo; mOS not reach *vs.* 9.4 mo
NCT06081959	OptiTROP-Breast02	III	Advanced	HR+/HER2− mBC	Sac-TMT *vs.* TPC	mPFS 8.3 *vs.* 4.1 mo; ORR 41.5% *vs.* 24.1%; mOS immature
NCT05445908	OptiTROP-Breast05	II	Advanced	mTNBC	Sac-TMT	ORR 70.7%; DCR 92.7%; mDOR 12.2 mo; mPFS 13.4 mo
NCT06279364	SKB264-III-11	III	Advanced	mTNBC	Sac-TMT *vs.* TPC	On going
ESG-401						
NCT04892342	/	I/II	Advanced	HER2− mBC (brain metastases)	ESG-401	IC-ORR 38%; IC-DCR 75%; ORR 50%; DCR 69%; mPFS 4.6 mo
F0024						
NCT05174637	/	I	Advanced	TNBC and other solid tumors	F0024	ORR 37.9%; DCR 79.3%

ADC, antibody-drug conjugate; CBR, clinical benefit rate; Dato-DXd, datopotamab deruxtecan; DCR, disease control rate; mDOR, median duration of response; EFS, event-free survival; HR+, hormone receptor-positive; iBCFS, invasive breast cancer-free survival; IC-DCR, intracranial disease control rate; IC-ORR, intracranial objective response rate; mBC, metastatic breast cancer; mo, months; mOS, median overall survival; mPFS, median progression-free survival; mTFST, median time to first subsequent therapy; mTNBC, metastatic triple-negative breast cancer; ORR, objective response rate; pCR, pathologic complete response; SG, sacituzumab govitecan; TPC, treatment of physician's choice; mTTR: median time to response; Sac-TMT: Sacituzumab tirumotecan.

Cross-trial observations suggested that Dato-DXd may have a safer hematologic profile than SG with markedly lower rates of severe neutropenia. This distinction could be clinically meaningful in patient selection.

Overall, Dato-DXd has rapidly become a new standard for mBC, while continuing to expand into earlier treatment settings, especially in TNBC. The ongoing phase III TROPION-Breast 03/04/05 trial is expected to benefit more patients.

Sacituzumab tirumotecan

Sac-TMT is an emerging TROP2 ADC that has gained approval in China and is generating promising results in global development. The results of the phase III **OptiTROP-Breast01** trial were presented at the 2024 American Society of Clinical Oncology (ASCO) meeting. This trial randomized 263 patients with pretreated mTNBC to Sac-TMT or chemotherapy.

Sac-TMT significantly improved the mPFS [6.7 *vs.* 2.5 months (HR = 0.32)] and ORR (45% *vs.* 12%); the OS benefit was not reached compared to 9.4 months for chemotherapy (HR = 0.53)[15]. The phase III OptiTROP-Breast02 trial (n = 399) showed that Sac-TMT significantly improved the mPFS [8.3 *vs.* 4.1 months (HR = 0.35)] in pretreated HR+/HER2− mBC with a higher 6-month PFS (61.4% *vs.* 25.7%) and ORR (41.5% *vs.* 24.1%) when compared to chemotherapy; a favorable early trend in OS was observed (HR = 0.33). These robust results highlight the potential of Sac-TMT as a strong competitor in the TROP2 ADC class[16].

Grade ≥ 3 AEs occurred in roughly 63% of patients in the Sac-TMT group. Hematologic toxicities, including neutropenia (35%), anemia (29%), and thrombocytopenia (13%), were the most common grade ≥ 3 AEs in patients treated with Sac-TMT. Stomatitis (any grade, 50%–60%) was the most common AE of special interest; 1 treatment-related death was reported. These data suggest that Sac-TMT offers a favorable efficacy–safety balance, although vigilance for hematologic and mucosal toxicities is warranted[16].

Emerging TROP2 ADCs

In addition to the three leading ADCs, several next-generation TROP2 ADCs are in early development in an effort to improve potency, stability, and safety. **ESG-401**, a phase I/II trial of HER2-negative mBC with central nervous system (CNS) involvement, achieved an intracranial ORR of 38% and intracranial disease control rate of 75%, with responses even in heavily pretreated patients[17]. Other ADC candidates, including **SHR-A1921**, **JS-108**, and **F0024**, are under preclinical or early clinical evaluation, leveraging novel payloads and linker designs to expand therapeutic reach.

Combination therapies with TROP2 ADCs

The success of TROP2 ADCs as monotherapies has opened the door to combination strategies aimed at amplifying therapeutic efficacy and overcoming resistance. Current strategies focus on pairing TROP2 ADCs with immune checkpoint inhibitors (ICIs), DNA damage repair inhibitors, and cell cycle regulators, with several key trials providing early insights (**Table 3**).

TROP2 ADCs and ICIs

TROP2 ADCs have been reported to induce immunogenic cell death (ICD), releasing tumor-associated antigens that stimulate immune responses. ICIs, such as PD-1/PD-L1 inhibitors, complement this effect by preventing T cell exhaustion and sustaining immune activation. The **BEGONIA trial** evaluated Dato-DXd plus durvalumab in mTNBC with any PD-L1 expression. The final results showed an ORR of 81.8%, mPFS of 14 months, and median DOR of 17.6 months, which far exceeded historical monotherapy outcomes[18]. Consistent findings from the phase III ASCENT-04 trial demonstrated that adding SG to pembrolizumab was superior to chemotherapy plus pembrolizumab. The SG combination regimen improved the mPFS [11.2 *vs.* 7.8 months (HR = 0.65)], a prolonged median DOR (16.5 *vs.* 9.2 months), and led to fewer treatment discontinuations (12% *vs.* 31%), collectively affirming the potent therapeutic synergy between TROP2-ADCs and ICIs[19].

The **SACI-IO HR+ trial** tested SG with or without pembrolizumab in HR+/HER2− disease. While the combination showed a modest improvement in mPFS [8.4 *vs.* 6.2 months (HR = 0.76)] and ORR (21% *vs.* 17%), the differences were not statistically significant. Safety profiles were comparable, although neutropenia was more frequent with the combination. Subgroup analyses based on TROP2 and PD-L1 expression may clarify which patients derive the greatest benefit[20].

PARP inhibitors: targeting DNA repair vulnerabilities

TROP2 ADCs inflict substantial DNA damage *via* cytotoxic payloads. When combined with PARP inhibitors, which impair the ability of the cancer cell to repair such damage, this strategy may induce synthetic lethality, thereby boosting antitumor effects. SG is currently being tested in combination with talazoparib and rucaparib in phase II trials for mTNBC. Early data suggest that the regimen is well-tolerated and shows promising antitumor activity, particularly in patients with limited treatment options[21]. Dato-DXd is also under investigation with AZD9574, a selective PARP inhibitor, in advanced solid tumors (NCT05417594). These dual-DNA damage approaches may yield more durable responses, particularly in BRCA-mutated or DDR-deficient patients.

CDK4/6 inhibitors: disrupting cell cycle progression

Resistance to CDK4/6 inhibitors is a major challenge in HR+/HER2− breast cancer. Combining these agents with TROP2 ADCs offers a complementary mechanism; specifically, CDK4/6 blockade induces cell cycle arrest, while ADCs deliver targeted cytotoxicity to TROP2-expressing cells. The ongoing NCT05113966 trial is exploring SG with a CDK4/6 inhibitor in patients with HR+/HER2− mBC who progressed on endocrine therapy and CDK4/6 inhibitors. This population has few

Table 3 Clinical developments of TROP2 ADCs as combined therapy in breast cancer treatment

NCT number	Study name	Phase	Combined compounds	Study design	Cancer status	Study population	Efficacy outcomes
Sacituzumab govitecan (SG)							
NCT05382286	ASCENT-04	III	ICI	SG + Pembro *vs.* TPC + Pembro	Advanced	mTNBC	mPFS 11.2 *vs.* 7.8 mo; ORR 59.7% *vs.* 53.2%; mDOR 16.5 *vs.* 9.2 mo
NCT05633654	ASCENT-05	III	ICI	SG + Pembro *vs.* capecitabine + Pembro	Early-adjuvant	TNBC	Ongoing
NCT04468061	SACI-IO TNBC	II	ICI	SG + Pembro *vs.* SG	Advanced	PD-L1− mTNBC	Ongoing
NCT04448886	SACI-IO HR+	II	ICI	SG + Pembro *vs.* SG	Advanced	PD-L1+/HR+/ HER2− mBC	mPFS 8.4 *vs.* 6.2 mo; mOS 16.9 *vs.* 17.1 mo; ORR 21.2% *vs.* 17.3%
NCT03971409	InCITe	II	ICI	Avelumab + binimetinib + liposomal doxorubicin *vs.* avelumab + SG *vs.* avelumab + liposomal doxorubicin	Advanced	mTNBC	Ongoing
NCT03424005	Morpheus-panBC	I/II	ICI	SG + Atezo *vs.* Nab-P + Atezo	Advanced	mTNBC	ORR 76.7% *vs.* 66.7%; mDOR 14.0 *vs.* 7.1 mo; mPFS 12.2 *vs.* 5.9 mo; CBR 83.3% *vs.* 66.7%
NCT04434040	ASPRIA	II	ICI	SG + Atezo	Early adjuvant	TNBC	Ongoing
NCT05675579	/	II	ICI	SG + Pembro	Early neoadjuvant	TNBC	Ongoing
NCT06081244	ADAPT-TN-III	II	ICI	SG + Pembro *vs.* SG	Early neoadjuvant	TNBC	Ongoing
NCT04958785	ELEVATE-TNBC	II	CD47 ADC	Magrolimab + nab-P *vs.* magrolimab + SG	Advanced	mTNBC	Ongoing
NCT04039230	/	I/II	PARPi	SG + talazoparib	Advanced	mTNBC	mPFS 6.2 mo; mOS 18 mo; ORR 30.1%; CBR at 6 mo 53.8%
NCT03992131	SEASTAR	I	PARPi	SG + rucaparib	Advanced	mTNBC	ORR 100%
NCT05113966	/	II	CDKi	Trilaciclib prior to SG	Advanced	mTNBC	ORR 23.3%; CBR 46.7%; mDOR 9.1 mo; mPFS 4.1 mo; mOS 17.9 mo
NCT05143229	ASSET	I	CDKi	SG + alpelisib	Advanced	HER2− mBC	Ongoing
Datopotamab deruxtecan (Dato-DXd)							
NCT03742102	BEGONIA	I/II	ICI	Dato-DXd + Durva	Advanced	mTNBC (any PD-L1 expression)	ORR 81.8%; mPFS 14 mo; mDOR 17.6 mo
NCT01042379	I-SPY2.2	II	ICI	Dato-DXd + Durva	Early neoadjuvant	HER2− BC	HR−/HER2−: pCR 62%
NCT05629585	TROPION-Breast03	III	ICI	Dato-DXd ± Durva *vs.* TPC	Early adjuvant	TNBC	Ongoing

Table 3 Continued

NCT number	Study name	Phase	Combined compounds	Study design	Cancer status	Study population	Efficacy outcomes
NCT06112379	TROPION-Breast04	III	ICI	Dato-DXd + Durva *vs.* TPC + Pembro	Early	TNBC or HR-low/ HER2-negative BC	Ongoing
NCT06103864	TROPION-Breast05	III	ICI	Dato-DXd ± Durva *vs.* TPC + Pembro	Advanced	PD-L1+ mTNBC	Ongoing
NCT04644068	PETRA	I	PARPi	Dato-DXd + AZD5305	Advanced	mBC cohort	Ongoing
NCT05417594	CERTIS1	I	PARPi	Dato-DXd + AZD9574	Advanced	mBC cohort	Ongoing
Sacituzumab tirumotecan (Sac-TMT)							
NCT06841354	TroFuse-011	III	ICI	Sac-TMT ± Pembro *vs.* TPC	Advanced	mTNBC	Ongoing
NCT06393374	TroFuse-012	III	ICI	Sac-TMT + Pembro *vs.* TPC	Early adjuvant	TNBC	Ongoing
NCT05445908	/	II	ICI	Sac-TMT + KL-A167 *vs.* Sac-TMT	Advanced	HER2− mBC	Ongoing
NCT07153965	/	II	ICI	Sac-TMT + tagitanlimab	Advanced	mTNBC	Ongoing
NCT07139470	/	II	TKI	Sac-TMT + anlotinib	Advanced	mTNBC	Ongoing
NCT07054242	/	II	ICI	Sac-TMT + Pembro	Early neoadjuvant	TNBC	Ongoing

ADC, antibody-drug conjugate; Atezo, atezolizumab; CBR, clinical benefit rate; CD47, cluster of differentiation 47; CDKi, cyclin-dependent kinase inhibitor; cfDNA, circulating free DNA; Dato-DXd, datopotamab deruxtecan; Durva, durvalumab; EFS, event-free survival; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor-positive; ICI, immune checkpoint inhibitor; mBC, metastatic breast cancer; mDOR, median duration of response; mo, months; mOS, median overall survival; mPFS, median progression-free survival; mTNBC, metastatic triple-negative breast cancer; nab-P, nab-paclitaxel; ORR, objective response rate; PARPi, poly(ADP-ribose) polymerase inhibitor; pCR, pathologic complete response; PD-L1, programmed death-ligand 1; Pembro, pembrolizumab; Sac-TMT, sacituzumab tirumotecan; SG, sacituzumab govitecan; TKI, tyrosine kinase inhibitor; TPC, treatment of physician's choice; TTD, time-to-deterioration.

treatment options and favorable results could establish a new standard in the post-CDK4/6 setting.

In addition to ICIs, PARP inhibitors, and CDK4/6 inhibitors, combining TROP2 ADCs with PI3K inhibitors or novel targeted agents are under early investigation. Collectively, these efforts aim to expand the reach of TROP2 ADCs, delay resistance, and improve outcomes across breast cancer subtypes.

Overcoming challenges in TROP2 ADC therapy

While TROP2-targeted ADCs have shown promising results in breast cancer, several challenges remain in optimizing TROP2-targeted ADC usage. Addressing these issues is essential to fully realizing the potential of this therapeutic class.

Safety and AE management

Balancing efficacy with tolerability remains a central consideration in TROP2-ADC therapy. SG is predominantly associated with hematologic toxicity, particularly neutropenia, which can be mitigated through dose modification, treatment delay, or granulocyte colony-stimulating factor (G-CSF) support. Dato-DXd exhibits a distinct profile characterized by stomatitis, fatigue, and low rates of interstitial lung disease, which are generally manageable with symptomatic care and early intervention. Mucositis and hematologic toxicities are the most frequent toxicities associated with Sac-TMT, reflecting the high DAR and potent topoisomerase payload. Gastrointestinal events, such as diarrhea and nausea, remain common across agents but are effectively controlled with antiemetics, antidiarrheals, hydration, and dietary adjustments[22]. As TROP2 ADCs move into earlier disease settings

and more diverse populations, proactive toxicity monitoring and supportive care will be essential to preserve treatment adherence and patient quality of life.

Resistance mechanisms and challenges

Several mechanisms of resistance have emerged. Downregulation or mutation of the *TACSTD2* gene reduces TROP2 surface expression, limiting ADC binding and uptake. Altered intracellular trafficking can prevent delivery of the conjugate to lysosomal compartments, thereby impairing payload release. In addition, enhanced activity of drug efflux pumps, such as ATP-binding cassette (ABC) transporters, may expel cytotoxic agents prematurely, reducing efficacy.

Emerging approaches to overcome resistance include dual-target ADCs co-recognizing TROP2 and HER3, payload diversification to evade ABC transporter efflux, and modulation of lysosomal trafficking through PI3K/AKT pathway inhibitors. Preclinical data suggest that combining TROP2 ADCs with PARP inhibitors or immune checkpoint blockade can restore cytotoxic activity in low-TROP2 or resistant clones, providing a rational path toward biomarker-guided combination therapy. Elucidating these mechanisms will be key to designing next-generation ADCs and combination strategies that overcome resistance, particularly in relapsed or refractory disease.

Biomarker development for patient selection

Effective biomarkers are urgently needed to optimize patient selection. Quantitative TROP2 expression correlates with clinical response to ADC therapy. Higher TROP2 H-scores were associated with improved ORR and PFS in the ASCENT and TROPION-Breast01 trial. Thus, TROP2 IHC may serve as a dual prognostic and predictive biomarker for patient selection. Ongoing research is investigating markers of DNA repair deficiency, immune activation, and drug resistance as potential predictors. Integrating such biomarkers into clinical decision-making could enable use of TROP2 ADCs in precision medicine, maximizing benefit while minimizing unnecessary exposure in patients unlikely to respond.

Innovative approaches and future directions

Because the field of ADCs is rapidly evolving, innovative approaches are being explored to enhance the efficacy, safety, and specificity of TROP2-targeted therapies.

Advanced ADC design

Innovations in ADC construction include more stable and tumor-specific linkers, which reduce premature payload release in circulation and minimize off-target toxicity. Newer cytotoxic payloads are being developed to overcome existing resistance mechanisms and to improve potency, even in low-antigen–expressing tumors[23]. Simultaneously, antibody engineering is enhancing binding affinity and selectivity, enabling more precise delivery of the therapeutic payload to cancer cells.

Extracellular vesicles

A particularly exciting innovation involves the use of extracellular vesicles (EVs), including exosomes, to improve ADC delivery. EVs can be engineered to carry ADCs or ADC components directly to tumor sites with high specificity, bypassing some of the limitations of traditional delivery methods. These strategies hold promise for resistant or poorly accessible tumors, where conventional ADC penetration is limited.

Personalized medicine

The integration of personalized medicine principles into ADC development is transforming treatment paradigms. By aligning therapies with the molecular profile of each patient's tumor, clinicians can enhance treatment efficacy while minimizing toxicity. This precision-guided approach is expected to become increasingly central in the deployment of TROP2 ADCs, particularly as more biomarkers and resistance mechanisms are uncovered.

Conclusions

TROP2-targeted ADCs have emerged as transformative class of therapeutics breast cancer, offering new hope for patients with limited treatment options. Ongoing efforts are focused on enhancing efficacy, expanding indications, and managing toxicities through improved design, smarter combinations, and better patient selection. As the field moves forward, TROP2 ADCs are poised to become a cornerstone of breast cancer therapy, bridging the gap between targeted precision and broad clinical utility.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Kuikui Jiang, Shusen Wang.
Collected the data: Kuikui Jiang.
Contributed data or analysis tools: Kuikui Jiang.
Performed the analysis: Kuikui Jiang.
Wrote the paper: Kuikui Jiang, Shusen Wang.

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