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Molecular Mechanisms of TROP2-Mediated Tumor Malignant Progression and Advances in ADC-Targeted Therapy

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Abstract. Trophoblast cell-surface antigen 2, encoded by TACSTD2, is a transmembrane glycoprotein with broad expression in epithelial malignancies and limited, compartmentalized expression in many normal adult tissues. Its tumor-associated distribution, rapid internalization, and functional connection with proliferation, epithelial-mesenchymal transition, stem-like phenotypes, chemoresistance, and survival signaling have made TROP2 both a biological driver and a therapeutic entry point. The clinical development of TROP2-directed antibody-drug conjugates has shifted the field from biomarker description toward target-enabled drug delivery. Sacituzumab govitecan established clinical proof of concept by coupling a TROP2 antibody with SN-38 through a hydrolysable linker, while datopotamab deruxtecan and sacituzumab tirumotecan illustrate newer strategies that refine payload chemistry, linker stability, drug-to-antibody ratio, and toxicity management. This review summarizes the molecular features and expression landscape of TROP2, the mechanisms through which TROP2 supports malignant progression, and the design logic and clinical status of representative TROP2-ADCs. Remaining issues include heterogeneous antigen expression, context-dependent signaling, payload resistance, lineage-specific toxicity, and the absence of standardized predictive assays. These issues frame the next stage of TROP2-targeted therapy.

Keywords: TROP2, TACSTD2, malignant progression, antibody-drug conjugate, sacituzumab govitecan, datopotamab deruxtecan

1. Introduction

TROP2 is a type I transmembrane glycoprotein encoded by TACSTD2 and was originally characterized in trophoblastic tissue before its broader role in epithelial biology and cancer became apparent. In malignant disease, TROP2 has attracted sustained interest because it combines two properties that are rarely aligned in one molecule. It is frequently overexpressed at the tumor cell surface, and it participates in signaling programs that support tumor growth, invasion, metastatic dissemination, and treatment adaptation. These features distinguish TROP2 from a passive lineage

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marker and explain why its therapeutic relevance extends beyond immunohistochemical detection [1, 2].

The rise of antibody-drug conjugates has changed how TROP2 is evaluated. Earlier work emphasized expression prevalence and associations with survival, while current studies examine antigen density, membrane localization, internalization, linker behavior, bystander killing, and resistance to topoisomerase I payloads. Sacituzumab govitecan demonstrated that TROP2-directed drug delivery can improve outcomes in metastatic breast cancer, and newer agents such as datopotamab deruxtecan and sacituzumab tirumotecan have expanded the design space for TROP2-ADCs [3-5]. This review follows the requested structure and discusses the molecular characteristics, tumor-promoting mechanisms, ADC design principles, clinical evidence, and unresolved barriers relevant to TROP2-targeted therapy.

2. Molecular features and tumor expression landscape of TROP2

2.1. Molecular structure and membrane localization of TROP2

As is shown in Figure 1,TROP2 consists of an extracellular domain, a single-pass transmembrane segment, and a short cytoplasmic tail. The extracellular region contains domains related to epithelial cell adhesion molecules, including a cysteine-rich portion and a thyroglobulin type-1-like region. Structural analysis indicates that TROP2 forms a stable dimer and differs from EpCAM in the membrane-distal region, a distinction that may influence antibody recognition and ligand-independent receptor behavior (Figure 1) [6]. Several therapeutic antibodies bind conformational or spatially restricted epitopes on the extracellular domain, making epitope accessibility, glycosylation, and membrane-proximal geometry relevant to ADC design [1].

Membrane localization is central to TROP2 biology. A target that remains intracellular or poorly accessible cannot support efficient antibody binding, even if total protein abundance is high. TROP2 is usually detected at the plasma membrane of epithelial tumor cells, although cytoplasmic staining can also appear in immunohistochemical studies. The cytoplasmic tail contains residues implicated in signal propagation and proteolytic processing. Cleavage-dependent release of intracellular fragments has been proposed as one route by which surface TROP2 connects extracellular recognition with nuclear or cytoplasmic signaling outputs [2, 7].

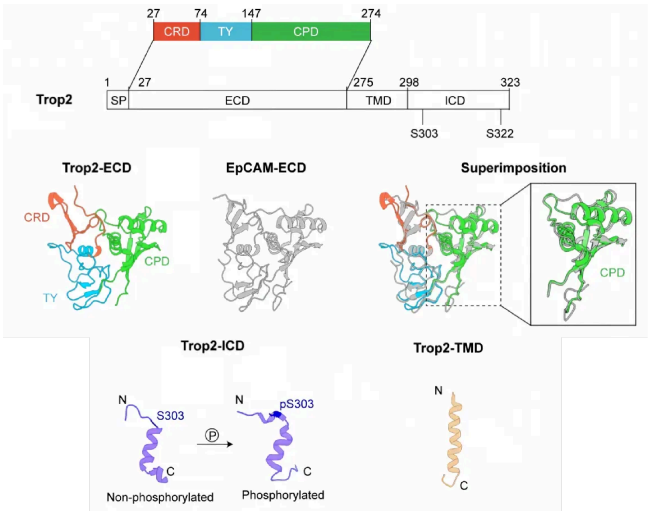

Figure 1. Molecular structure and membrane localization of TROP2 [1]

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The structural relationship between TROP2 and EpCAM also has practical consequences for antibody selection. Sequence homology does not guarantee equivalent epitope conformation, and small differences in the extracellular region can alter antibody binding, receptor clustering, and ADC internalization. For this reason, epitope mapping has become more than a descriptive exercise. It helps distinguish antibodies that simply label TROP2-positive cells from antibodies that support efficient uptake and intracellular delivery. The same issue applies to glycosylation, because carbohydrate modification can change steric exposure of the protein surface and may differ between normal epithelium and malignant tissue [1, 6].

2.2. Physiological function and normal tissue expression of TROP2

In normal tissues, TROP2 is mainly associated with epithelial compartments, progenitor-like states, tissue repair, and barrier maintenance. Its expression is not absent from healthy organs, which is important for ADC safety evaluation. The difference between physiologic and malignant expression is often quantitative, spatial, and contextual rather than binary. In adult tissues, expression tends to be restricted to epithelial surfaces, while many carcinomas show stronger and more diffuse membrane staining. This distribution supports a therapeutic window but does not eliminate on-target toxicity, particularly in tissues with epithelial turnover [2].

The physiological functions of TROP2 remain less completely defined than its pathological associations. Data from structural and cellular studies suggest roles in epithelial organization, calcium-related signaling, cell-cell interactions, and regulation of proliferative states. These functions are compatible with the observation that tumors arising from epithelial lineages often retain or amplify TROP2 expression. A cautious interpretation is needed because TROP2 may act as a context-dependent signaling modulator rather than as a single canonical receptor with one dominant ligand or pathway [2, 7].

2.3. Aberrant expression of TROP2 in malignant tumors

Aberrant TROP2 expression has been reported across breast, lung, urothelial, gynecologic, gastrointestinal, pancreatic, head and neck, and other epithelial cancers. Studies in gastrointestinal tumors and urothelial carcinoma support an association between high TROP2 expression and adverse clinical features, although the magnitude of association varies by tumor type, assay platform, antibody clone, scoring method, and treatment setting [8, 9]. This variability has practical consequences. A tumor may be considered TROP2 positive by one assay but show insufficient membrane antigen density for an ADC response in another clinical context.

Expression heterogeneity occurs between tumor types, between patients with the same diagnosis, and within individual lesions. Metastatic sites can differ from primary tumors, and prior systemic therapy may alter antigen expression or select subclones with distinct TROP2 levels. For ADC development, heterogeneous expression does not always preclude activity because membrane-permeable payloads can produce bystander effects after linker cleavage. It can, however, reduce the probability of homogeneous payload delivery and may contribute to mixed responses or early progression [3, 10].

2.4. Clinicopathological significance and prognostic value of TROP2 expression

High TROP2 expression has been linked to advanced stage, lymph-node involvement, invasion, recurrence, and inferior survival in several solid tumors. Systematic work in gastrointestinal

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malignancies supports a negative prognostic association, while studies in urothelial carcinoma and other cancers suggest that TROP2 expression can accompany aggressive histology or metastatic behavior [9]. These correlations do not by themselves establish that TROP2 is an independent driver in every tumor type. They do indicate that TROP2 expression marks biologically active epithelial cancer states and may enrich for tumors capable of responding to TROP2-directed delivery.

The clinical use of TROP2 as a predictive biomarker remains unsettled. Sacituzumab govitecan and datopotamab deruxtecan have shown activity in populations not always selected by strict TROP2 expression thresholds, suggesting that antigen presence above a permissive level may be sufficient for some patients. Conversely, low antigen density, cytoplasmic-predominant staining, or spatial heterogeneity could limit ADC uptake. Standardized assays will be needed before TROP2 can function as a reliable selection marker across drugs, payloads, and tumor types [5].

3. Molecular mechanisms of TROP2-mediated malignant tumor progression

3.1. Regulation of tumor cell proliferation, survival, and cell cycle progression by TROP2

TROP2 supports tumor cell proliferation through signaling networks that converge on survival and cell-cycle machinery. TROP2 has been proved to be linked with several molecular mechanisms ,including PI3K-AKT, MAPK-ERK, cyclin D1, beta-catenin-related transcription, and calcium-dependent signaling modules， which are summarized in Figure 2. These pathways can increase entry into the cell cycle, reduce apoptotic priming, and maintain growth under stress (Figure 2). The effect is not uniform across tumor lineages, which suggests that TROP2 amplifies pre-existing oncogenic circuitry rather than replacing lineage-specific driver alterations.

The relationship between TROP2 and survival signaling also has therapeutic implications. Tumors with high TROP2 expression may be more dependent on epithelial growth programs, but the same tumors can maintain redundant pathways downstream of receptor tyrosine kinases, PI3K, RAS, or WNT. This redundancy helps explain why direct blockade of TROP2 signaling has been less clinically mature than ADC-based drug delivery. In practice, TROP2 is exploited less as a single signaling switch and more as a membrane address that carries cytotoxic payloads into tumor cells [3, 5, 11].

3.2. Promotion of epithelial-mesenchymal transition, invasion, and metastasis by TROP2

TROP2 has been associated with epithelial-mesenchymal transition, invasion, and metastatic spread. Mechanistic studies connect TROP2 expression with reduced epithelial adhesion, enhanced motility, extracellular matrix remodeling, and activation of signaling nodes that regulate EMT transcriptional programs [2, 10]. These effects are consistent with clinical correlations between high TROP2 levels and nodal involvement or advanced disease in several carcinomas [9, 12]. The biological pattern is best viewed as an interaction between membrane signaling, cytoskeletal remodeling, and lineage-specific transcriptional states.

Metastatic progression depends on more than migration. Tumor cells must survive detachment, resist anoikis, invade stromal tissue, enter and exit the circulation, and adapt to distant microenvironments. TROP2-related signaling may contribute to several of these steps through survival pathways and maintenance of epithelial plasticity. The same plasticity can complicate treatment, because cells that transition between epithelial and mesenchymal states may alter antigen distribution, endocytosis, and sensitivity to DNA-damaging payloads [10, 13].

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3.3. TROP2, tumor stemness, recurrence, and treatment tolerance

TROP2 expression has been linked with progenitor-like and stem-like properties in epithelial malignancies. Tumor cells with stem-like traits often show enhanced repair capacity, slow cycling states, and resistance to cytotoxic stress. TROP2 may participate in these phenotypes by supporting survival signaling, epithelial lineage plasticity, and adaptation to therapy-induced pressure [2, 10]. These associations help explain why TROP2 is frequently discussed in the setting of recurrence and residual disease rather than only in untreated primary tumors.

Chemoresistance adds another layer to the biology of TROP2. Reviews of TROP2 and chemotherapeutic response describe links between TACSTD2 expression, DNA damage response, apoptotic thresholds, drug efflux, and resistance to conventional agents [13]. These observations do not imply that TROP2 alone determines therapeutic failure. They indicate that TROP2-positive tumors may carry cellular states that tolerate treatment and that ADC response will depend on payload sensitivity, intracellular release, and target persistence. The emergence of resistance to TROP2-ADCs confirms that antigen delivery and payload vulnerability must both be preserved [14, 15].

3.4. TROP2-related signaling pathways and tumor microenvironment regulation

TROP2-related signaling intersects with pathways that shape the tumor microenvironment. AKT, ERK, beta-catenin, and calcium-associated signals can influence cytokine production, epithelial barrier behavior, stromal communication, and immune exclusion in tumor tissue (Figure 2) [2, 10]. The evidence is still more developed at the tumor-cell level than at the ecosystem level. A measured interpretation is that TROP2-positive cells may contribute to a microenvironment favorable to invasion and persistence, while stromal and immune factors may in turn modulate TROP2 expression and ADC delivery.

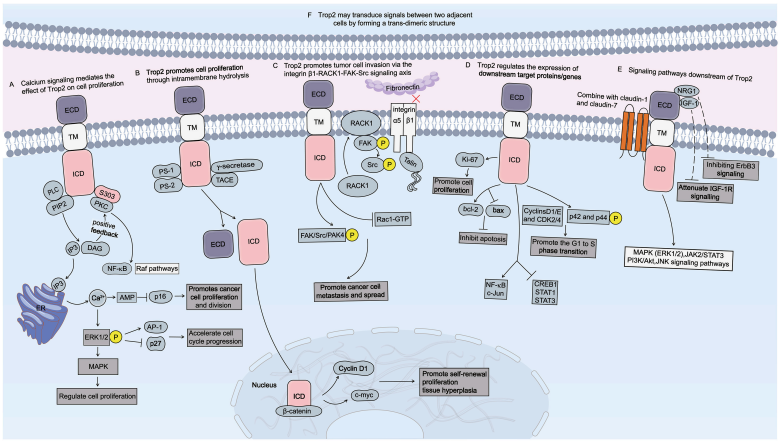

Figure 2. Molecular mechanisms of TROP2-mediated tumor progression [10]

The microenvironment also affects ADC pharmacology. Dense stroma, vascular permeability, interstitial pressure, antigen heterogeneity, and lysosomal function can determine how much antibody reaches tumor cells and how effectively payload is released. ADCs with membrane-permeable topoisomerase I inhibitors may partially overcome spatial heterogeneity through bystander killing, but this mechanism can also contribute to toxicity if linker cleavage and payload

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diffusion are insufficiently confined. TROP2 biology and ADC pharmacology need to be evaluated together rather than in separate compartments [3, 5, 11].

4. Drug design, mechanism of action, and clinical application of TROP2-ADCs

4.1. Biological basis for TROP2 as an ADC target

A suitable ADC target should be accessible on the tumor cell surface, sufficiently enriched in cancer relative to vulnerable normal tissues, capable of antibody binding and internalization, and biologically stable during treatment. TROP2 satisfies many of these requirements across epithelial tumors [1, 2, 11]. Its expression on the plasma membrane allows antibody engagement, and internalization enables lysosomal or intracellular release of payload. The target is not tumor-specific, but the therapeutic index of ADCs can be improved through linker chemistry, payload potency, dosing schedule, and patient selection [3, 16].

TROP2 also offers a broad clinical development platform because its expression spans multiple tumor types. This breadth supports basket-like exploration but also creates a risk of overgeneralization. Tumor lineage, prior therapy, antigen density, proliferation rate, DNA repair capacity, and topoisomerase I dependence can all affect response. A target that performs well in metastatic breast cancer may not produce the same benefit in lung, urothelial, or gastrointestinal tumors without appropriate drug design and clinical positioning [10, 17, 18].

4.2. Structural components and drug design strategies of TROP2-ADCs

TROP2-ADCs combine an anti-TROP2 antibody, a chemical linker, and a cytotoxic payload. Figure 3 shows that Sacituzumab govitecan consists of a humanized anti-TROP-2 antibody linked to SN-38, the active metabolite of irinotecan, through a hydrolysable CL2A linker with a relatively high drug-to-antibody ratio [11]. This structure supports payload release both after internalization and in the tumor microenvironment, creating a bystander effect t24hat may be useful in heterogeneous tumors. The same design can contribute to neutropenia and diarrhea, toxicities consistent with systemic exposure to SN-38 [11, 17, 19].

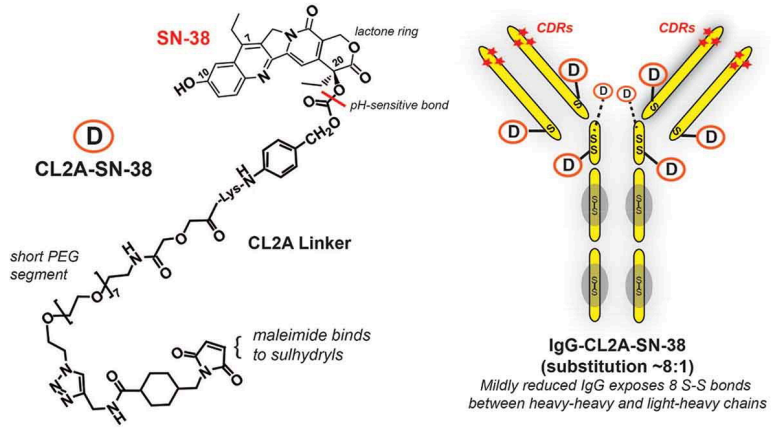

Figure 3. The structural components of Sacituzumab govitecan [11]

Datopotamab deruxtecan uses a TROP2 antibody connected to a deruxtecan topoisomerase I inhibitor payload through a cleavable tetrapeptide linker. Preclinical studies showed potent tumor-cell delivery and antitumor activity, while clinical studies have emphasized activity in breast cancer

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and non-small-cell lung cancer [20, 21]. Sacituzumab tirumotecan represents another design, using a TROP2 antibody linked to a belotecan-derived topoisomerase I inhibitor through a cleavable linker. Its development illustrates the current movement toward payload and linker optimization rather than simple replication of the first successful TROP2-ADC [22, 23].

4.3. Endocytic delivery, payload release, and antitumor mechanisms of TROP2-ADCs

After binding to TROP2, an ADC can be internalized and trafficked through endosomal and lysosomal compartments, where proteolysis or chemical cleavage releases active payload. Topoisomerase I inhibitors create DNA single-strand breaks that convert into lethal damage during replication, making proliferating tumor cells especially vulnerable. Membrane-permeable payloads can diffuse into neighboring antigen-low cells and produce bystander killing. This feature is relevant for TROP2-positive tumors with heterogeneous antigen expression [3, 5, 11].

The antitumor effect of TROP2-ADCs depends on several sequential steps. Antibody binding requires accessible membrane antigen. Internalization and trafficking determine intracellular payload delivery. Linker stability controls the balance between tumor release and systemic exposure. Payload sensitivity depends on topoisomerase I biology, DNA repair capacity, replication stress, and drug efflux. Failure at any step can reduce efficacy even when TROP2 staining appears strong [3].

These sequential requirements explain why ADC activity cannot be inferred from surface expression alone. A tumor with high TROP2 staining may respond poorly if endocytic trafficking is inefficient, lysosomal processing is altered, or the released payload is neutralized by repair and efflux programs. A tumor with intermediate antigen density may still respond when linker cleavage, payload permeability, and replication stress favor bystander killing. Pharmacodynamic assessment of DNA damage, circulating payload exposure, and paired biopsies before and after treatment could help separate antigen failure from payload failure in clinical studies [14].

4.4. Representative TROP2-ADC drugs and clinical research progress

Sacituzumab govitecan established the clinical proof of concept for TROP2-directed ADC therapy. In the ASCENT trial, it improved progression-free and overall survival compared with single-agent chemotherapy in previously treated metastatic triple-negative breast cancer [17].In TROPiCS-02, sacituzumab govitecan improved outcomes in endocrine-resistant hormone receptor-positive and HER2-negative metastatic breast cancer after prior systemic therapy [19]. Activity in urothelial carcinoma was demonstrated in TROPHY-U-01, although later development in that indication illustrates the need for confirmatory benefit beyond response rate [24].

Datopotamab deruxtecan has produced clinically meaningful activity in non-small-cell lung cancer and breast cancer. TROPION-PanTumor01 reported activity in previously treated non-small-cell lung cancer and in advanced breast cancer cohorts [21, 25]. TROPION-B23 reast01 showed superiority over investigator's choice chemotherapy in previously treated hormone receptor-positive and HER2-negative metastatic breast cancer [26]. TROPION-Lung01 compared datopotamab deruxtecan with docetaxel in previously treated advanced non-small-cell lung cancer and demonstrated an efficacy signal with a toxicity profile shaped by mucosal and interstitial lung disease risks [18].

Sacituzumab tirumotecan has added another clinical dimension to the TROP2-ADC field. Phase 1 and 2 studies in refractory solid tumors showed antitumor activity across selected tumor types [22]. A randomized phase 3 trial in previously treated metastatic triple-negative breast cancer reported improved efficacy compared with chemotherapy, and studies in advanced non-small-cell lung cancer

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with or without EGFR mutations have further extended its development program [23, 27]. These data suggest that TROP2-ADC therapy is becoming a drug class rather than a single-agent phenomenon.

4.5. Therapeutic limitations, resistance mechanisms, and optimization strategies for TROP2-ADCs

The main limitations of TROP2-ADCs include heterogeneous antigen expression, toxicities related to topoisomerase I payloads, uncertain predictive biomarkers, and acquired resistance. Sacituzumab govitecan resistance has been associated with genomic alterations affecting both TACSTD2 and TOP1, demonstrating that tumors can escape by reducing antigen-mediated delivery or by altering the payload target [14]. Broader ADC resistance mechanisms include impaired internalization, altered lysosomal processing, drug efflux, enhanced DNA repair, lineage plasticity, and selection of antigen-low clones [15].

Optimization strategies are likely to differ by drug and tumor type. Linkers can be tuned to reduce premature release while preserving bystander killing. Payloads can be diversified beyond topoisomerase I inhibition to address cross-resistance. Antibody engineering may improve epitope binding, internalization, or pharmacokinetics. Combination therapy with DNA damage response inhibitors, immunotherapy, endocrine therapy, or pathway inhibitors requires careful sequencing because toxicity may overlap with payload-related adverse events. Biomarker development should measure membrane TROP2, spatial heterogeneity, TOP1 status, DNA repair features, and prior exposure to topoisomerase I-based ADCs rather than relying on a single immunohistochemical cutoff [28, 29].

Toxicity management is part of the same optimization problem. Neutropenia, diarrhea, stomatitis, ocular events, and interstitial lung disease do not arise from one universal mechanism across TROP2-ADCs. They reflect payload class, linker stability, tissue exposure, host metabolism, and sometimes pharmacogenetic factors such as UGT1A1 variants for SN-38 exposure [28]. Trial design should distinguish adverse events caused by antigen distribution from those caused by systemic payload release. This distinction matters when choosing between dose reduction, schedule modification, prophylactic supportive care, or a switch to an ADC with a different linker-payload system.

5. Conclusions and outlook

TROP2 links epithelial tumor biology with ADC-based pharmacology. Its membrane localization, frequent overexpression, internalization capacity, and involvement in proliferative, invasive, stem-like, and treatment-tolerant states provide a biological basis for therapeutic targeting. The most mature clinical results come from topoisomerase I payload ADCs, especially sacituzumab govitecan, datopotamab deruxtecan, and sacituzumab tirumotecan. Their development has shown that TROP2 is not merely a marker of epithelial cancers but a useful route for cytotoxic delivery in selected disease settings.

Several practical questions remain. It is still unclear whether TROP2 expression should be measured by one universal assay or by drug-specific companion approaches. The optimal sequencing of TROP2-ADCs after prior topoisomerase I ADC exposure is also unresolved. Cross-resistance may depend on whether progression was driven by antigen loss, TOP1 alteration, drug efflux, or microenvironmental delivery failure. Trials that collect tissue, blood, and pharmacokinetic data at progression will be more informative than trials that record response duration alone.

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The next stage of TROP2 research should refine the connection between target biology and drug response. Current evidence supports neither unrestricted treatment of all TROP2-expressing tumors nor a narrow view in which a single staining threshold determines eligibility. Better assays must capture membrane antigen density, intratumoral heterogeneity, internalization competence, payload sensitivity, and resistance after prior ADC exposure. Clinical development will also need to clarify sequencing among TROP2-ADCs, HER2-directed ADCs, immune checkpoint inhibitors, endocrine therapy, chemotherapy, and targeted agents. A durable role for TROP2-directed therapy will depend on matching ADC design to tumor biology rather than treating TROP2 expression as a uniform therapeutic label.

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