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REVIEW

Antibody–drug conjugates in solid tumors: Efficacy, challenges, and opportunities

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Antibody–drug conjugates (ADCs) have become an increasingly important component of the therapeutic landscape of many solid tumors. Currently, there are eight ADCs approved for solid tumors, with hundreds being developed and in clinical trials. Initially being approved in the advanced or metastatic settings, ADCs are also being incorporated as neoadjuvant or adjuvant therapies. In this review, we discuss the important components of ADC design in the context of clinical successes and failures. We further evaluate mechanisms of intrinsic and acquired resistance and strategies to overcome these barriers. Finally, we discuss the landscape of potential combination partners to increase efficacy of ADC therapies.

Introduction

Antibody–drug conjugates (ADCs) have revolutionized the treatment landscape for patients with solid tumors, precipitating a surge in research, development, and innovation. They have been coined "biological missiles," combining the precise targeting of a monoclonal antibody with the potent cytotoxicity of the attached payload (Yao et al., 2026; Fu et al., 2022; Veneziani et al., 2024). There are currently eight Food and Drug Administration (FDA)-approved ADCs in solid tumors (Wang et al., 2025b; Camidge et al., 2024), and numerous ADCs are currently in development and in clinical trials (Zhou et al., 2024a). ADCs were initially developed more than four decades ago, and they suffered many setbacks until the first ADC for solid tumors was approved in 2013; hundreds of ADCs have been discontinued (Colombo et al., 2024). Important innovations in target discovery, antibody engineering, linker design, and payloads led to the development of currently successful ADC programs. In this review, we highlight characteristics of approved ADCs that have led to their success, describe pitfalls and resistance mechanisms that limit their efficacy, and explore strategies to overcome these barriers. We first discuss important design considerations of ADCs and their impact on the success and failure of clinical programs. We further explore mechanisms of intrinsic and acquired resistance. Finally, in the context of these limitations, we discuss how combination strategies with ADCs and future innovations may address current limitations and continue to expand the efficacy of these promising agents.

Current ADC targets

Broadly, ADCs consist of an antibody to a tumor-enriched target that is linked to a therapeutic payload. However, each aspect of the ADC design—the antibody (and target), conjugation strategy, linker type, and payload—must be carefully considered in developing a successful agent. Trastuzumab emtansine was the first ADC to receive FDA approval for a solid tumor in February 2013 (Verma et al., 2012), and there have been seven additional ADCs that have FDA approval for solid tumors targeting six cell surface proteins. In this section, we will briefly discuss each target and each approved ADC.

Human EGF receptor 2 (HER2)

HER2 is a member of the EGF receptor (EGFR) family of receptor tyrosine kinases. Heterodimerization with other members of the EGFR family leads to autophosphorylation of tyrosine residues and activates various pathways that lead to cell proliferation, survival, and tumorigenesis. When overexpressed in preclinical models, it leads to increases in mitogenic and cell cycle signaling (Zhou and Agazie, 2012). HER2 is expressed across a diverse range of cancer types (Uzunparmak et al., 2023) and is the only target that has a therapy with tumor-agnostic approval (Shah and Meric-Bernstam, 2025).

Trastuzumab emtansine (T-DM1)

T-DM1 is a HER2-targeting IgG1 monoclonal antibody with a noncleavable linker that is attached to mertansine (DM1), a maytansine derivative that is a potent microtubule-targeting compound and membrane impermeable (Lambert and Chari, 2014; Erickson et al., 2006). Lysine conjugation is used in production, and the drug-to-antibody ratio (DAR) is ∼3.5 (Poon et al., 2013). T-DM1 is approved for HER2-positive (HER2 3$^+$ or HER2 2$^+$/ISH positive) metastatic breast cancer for patients that have previously received trastuzumab and a taxane

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(Verma et al., 2012). Trastuzumab deruxtecan (T-DXd) showed superiority in this setting in a subsequent trial and is now the preferred agent (Cortés et al., 2022). T-DM1 is also approved in the adjuvant setting for patients with HER2-positive breast cancer with residual disease after receiving neoadjuvant trastuzumab and taxane-based regimens (von Minckwitz et al., 2019). Recently, T-DXd has also shown superiority to T-DM1 for high-risk residual disease (Loibl et al., 2026). Notable high-grade toxicities of T-DM1 seen in trials include thrombocytopenia, liver toxicity, and cardiac events (von Minckwitz et al., 2019).

Trastuzumab deruxtecan (T-DXd)

T-DXd is a HER2-targeting IgG1 monoclonal antibody with an enzyme-cleavable linker that is attached to DXd, a potent camptothecin derivative that is a topoisomerase 1 inhibitor that is membrane permeable (Ogitani et al., 2016b). Interchain cysteine conjugation is used in production, and the DAR is ∼7.7 (Ogitani et al., 2016a). T-DXd has the most approved indications of any ADC that spans across histologies and levels of HER2 expression. T-DXd first achieved accelerated approval for HER2-positive (HER2 3^+ or HER2 2^+/ISH positive) unresectable or metastatic breast cancer for patients previously treated with T-DM1. Subsequently, in the DESTINY-Breast03 phase 3 trial, T-DXd showed improved clinical outcomes compared with T-DM1 and achieved FDA approval in patients with unresectable/metastatic breast cancer with previous treatment of trastuzumab and taxane or those that had recurred within 6 mo of neoadjuvant treatment (Cortés et al., 2022). Recently, T-DXd plus pertuzumab have been FDA approved as first-line therapy for patients with advanced or metastatic $HER2^+$ breast cancer (Tolaney et al., 2026). T-DXd has also had recent approvals in the perioperative setting. For patients with HER2-positive breast cancer with high-risk residual disease, defined as nonoperable disease at presentation or operable disease that is axillary-node positive, T-DXd has been approved showing superiority to T-DM1 after neoadjuvant therapy with anti-HER2 therapy and taxane-based chemotherapy (Geyer et al., 2025). Furthermore, T-DXd is also approved in the neoadjuvant setting for patients with stage II or III HER2-positive breast cancer, followed by the combination of a taxane, trastuzumab, and pertuzumab (Harbeck et al., 2026).

In hormone-positive breast cancer, T-DXd has further been approved in HER2-low (HER2 2^+/ISH^- or HER2 1^+) breast cancer that has received prior chemotherapy in metastatic setting or had recurrence within 6 mo of adjuvant chemotherapy (Modi et al., 2022). In addition, most recently, it has also been approved in the HER2 low and ultralow setting (HER2 0 with >0% and ≤10% invasive cancer cells showing incomplete membrane staining) after endocrine therapy (Bardia et al., 2024a).

Outside of breast cancer, T-DXd also received accelerated approval in HER2-positive gastric cancer (Shitara et al., 2020) and non-small cell lung cancer (NSCLC) with *HER2* mutations (Goto et al., 2023). T-DXd is also the only ADC with tumor agnostic approval for patients with HER2-positive (IHC 3^+) solid tumors based on data from three trials, including the DESTINY-PanTumor-02 basket trial that included multiple histologies (Raghav et al., 2024; Smit et al., 2024; Meric-Bernstam et al., 2024). Important high-grade toxicities recognized across clinical trials include cardiotoxicity, interstitial lung disease, cytopenias, and gastrointestinal (GI) toxicities (Pathak et al., 2025).

Trophoblast cell surface antigen-2 (TROP2)

TROP2 is a cell surface glycoprotein that activates numerous pathways associated with cell proliferation, invasion, and metastasis. Consistent with its involvement in a variety of cancer-associated signaling pathways, overexpression of TROP2 has been reported and linked to poor prognosis in many tumors of epithelial origin, including pancreatic, gastric, and cervical cancers (Zhao et al., 2015; Zeng et al., 2016; Ning et al., 2013; Liu et al., 2013; Fong et al., 2008). Gene expression analyses have shown upregulation of TROP2 in cancerous tissues compared with their matching normal tissues across a broad spectrum of solid tumors (Trerotola et al., 2013). Through these findings, TROP2 has become a highly attractive therapeutic target on the cell surface.

Sacituzumab govitecan (SG)

SG is a TROP2-targeting IgG1 monoclonal antibody with a pH-sensitive linker that is attached to SN-38, the active metabolite of irinotecan that is a potent topoisomerase 1 inhibitor that is membrane permeable (Cardillo et al., 2015). Interchain cysteine conjugation is used in production, and the DAR is ∼7.6 (Cardillo et al., 2015). SG first received FDA approval in patients with relapsed or refractory metastatic triple-negative breast cancer (TNBC) (Bardia et al., 2021a). Subsequently, SG was approved in patients with hormone receptor (HR)-positive and HER2-negative breast cancer that have received at least one previous line of endocrine therapy, a taxane, and a CDK4/6 inhibitor and at least two previous lines of chemotherapy (Rugo et al., 2023). Of note, SG initially received accelerated approval in metastatic urothelial cancer based on promising phase II activity (Loriot et al., 2024); however, lack of survival benefit and increased rates of treatment-related adverse events, mostly from neutropenia, resulting in death in the confirmatory trial led to withdrawal (Powles et al., 2025). ADCs are not necessarily always less toxic than systemic chemotherapy, and prophylaxis of significant toxicities needs to be carefully considered. Major adverse events with SG include neutropenia (high-risk patients should have G-CSF prophylaxis), nausea, and diarrhea (Schlam et al., 2023).

Datopotamab DXd (Dato-DXd)

Dato-DXd is a TROP2-targeting IgG1 monoclonal antibody with an enzyme-sensitive linker that is attached to the topoisomerase I inhibitor payload DXd (Okajima et al., 2021). Interchain cysteine conjugation is used in production, and the DAR is ∼4 (Okajima et al., 2021). For patients with HR^+/$HER2^-$ inoperable/metastatic breast cancer that had progressed on endocrine therapy and one to two lines of chemotherapy, Dato-DXd received accelerated approval based on superiority compared with chemotherapy in this setting (Bardia et al., 2025). For patients with metastatic TNBC ineligible for immunotherapy, first-line Dato-DXd has also recently been approved (Dent et al., 2026). Currently, Dato-DXd is also in neoadjuvant and adjuvant therapy

trials for breast cancer (Bardia et al., 2024b; Shatsky et al., 2024). Dato-DXd also received accelerated approval for patients with *EGFR*-mutated NSCLC that had received previous EGFR-directed therapy and platinum-based chemotherapy (Ahn et al., 2025; Sands et al., 2025). Important toxicities that require monitoring and prophylaxis include stomatitis and ocular surface events (Heist et al., 2024).

Nectin cell adhesion molecule 4 (NECTIN4)

NECTIN4 is canonically involved in cell adhesion. In normal conditions, expression of NECTIN4 is restricted to the embryo and placenta with low-level expression in most adult tissues (Li et al., 2024; Challita-Eid et al., 2016). NECTIN4 IHC staining showed positivity in numerous tumor types that include bladder, breast, pancreatic, lung, ovarian, head and neck, and esophageal cancer (Challita-Eid et al., 2016). In transformation of epithelial cells, NECTIN4 plays an important role in allowing for anchorage-independent growth seen in early stages of progression, and its knockdown can prevent tumor growth (Pavlova et al., 2013).

Enfortumab vedotin (EV)

EV is a NECTIN4-targeting IgG1 monoclonal antibody with an enzyme-sensitive linker that is attached to vedotin, a monomethyl auristatin E (MMAE) microtubule-disrupting payload that is membrane permeable. Interchain cysteine conjugation is used in production, and the DAR is ∼4 (Challita-Eid et al., 2016). EV is approved for locally advanced or metastatic urothelial cancer in combination with pembrolizumab as first-line therapy (Thomas et al., 2024). Recently, EV plus pembrolizumab also received approval as perioperative treatment for patients with muscle invasive bladder cancer that are not eligible for cisplatin (Center for Drug Evaluation and Research, 2025). Important toxicities to monitor for include neuropathy, skin toxicities, and GI toxicities (Lacouture et al., 2022).

Folate receptor 1 (FOLR1)

FOLR1 is a glycosylphosphatidylinositol-anchored protein that is involved in folate transportation and is capable of reducing folates. In normal tissues, FOLR1 is expressed on the apical surfaces of the lung, kidney, choroid plexus, and placenta (Varaganti et al., 2023). It is overexpressed in multiple cancer types that include ovarian cancer, uterine cancer, pancreatic cancer, biliary tract cancer, testicular germ cell tumors, and glioblastoma (Nawaz and Kipreos, 2022; Liu et al., 2025b). Though some studies have shown association with poor prognosis (Liu et al., 2020), these results are not consistent (Köbel et al., 2014). The exact role of FOLR1 in tumorigenesis has not been established (Nawaz and Kipreos, 2022).

Mirvetuximab soravtansine

Mirvetuximab soravtansine is a FOLR1-targeting IgG1 monoclonal antibody with an enzyme-sensitive linker that is attached to DM4, a maytansine derivative that is a potent microtubule targeting compound that is membrane permeable (Ab et al., 2015; Ponte et al., 2016). Lysine conjugation is used in production, and the DAR is ∼3.5 (Tu et al., 2024). In the MIRASOL phase 3 trial, patients with high-grade serous ovarian cancer and high FOLR1 expression (≥75% tumor cells with ≥2+ staining) were randomized to receive mirvetuximab soravtansine or chemotherapy, and mirvetuximab soravtansine showed improved progression-free survival (PFS) and overall survival (OS) and received FDA approval for this indication (Moore et al., 2023). Major toxicities include ocular surface events, GI toxicities, and neuropathy (Lang et al., 2025).

Tissue factor (TF)

TF is an important part of the coagulation cascade and is the receptor and cofactor for FVIIa. After tissue injury or trauma, The TF–FVIIa complex can trigger the coagulation cascade (Grover and Mackman, 2018). In cancer, it is associated with angiogenesis and invasion and can lead to activation of multiple proliferative pathways through its binding and cleavage activities (Ahmadi et al., 2023; Hassan et al., 2023). It is upregulated in many cancer types (de Bono et al., 2023).

Tisotumab vedotin

Tisotumab vedotin is a TF-targeting IgG1 monoclonal antibody with an enzyme-sensitive linker that is attached to vedotin, a MMAE microtubule-disrupting payload that is membrane permeable. Interchain cysteine conjugation is used in production, and the DAR is ∼4 (Breij et al., 2014). In the phase 3 innovaTV-301 trial, tisotumab vedotin displayed improved PFS compared with the investigator's choice of chemotherapy for patients with recurrent or metastatic cervical cancer as second- or third-line therapy and received FDA approval. Major toxicities of tisotumab vedotin include ocular surface events, anemia, and GI toxicities (Vergote et al., 2024).

MET

The hepatocyte growth factor receptor (MET) is a tyrosine kinase that is physiologically involved in wound healing and embryonic development (Chmielowiec et al., 2007; Zhao et al., 2022; Latimer and Jessen, 2008). It activates many proliferative pathways through activation from binding its ligand or ligand-independent activation of MET through interaction with partners such as integrins and fibronectin (Huang et al., 2025; Mitra et al., 2011). MET is expressed in various normal adult tissues and is overexpressed across various solid tumor (Li et al., 2020b). MET amplification can also derive resistance to therapies targeting other receptor tyrosine kinases such as EGFR inhibitors (Chmielecki et al., 2023).

Telisotuzumab vedotin

Telisotuzumab vedotin is a MET-targeting IgG1 monoclonal antibody with an enzyme-sensitive linker that is attached to vedotin, a MMAE microtubule–disrupting payload that is membrane permeable. Interchain cysteine conjugation is used in production, and the DAR is ∼3 (Wang et al., 2017b). In the phase 2 LUMINOSITY trial, patients with non-squamous, *EGFR*-wild type NSCLC with previous treatment and cMET overexpression (≥50% tumor cells with 3+ expressions) were treated with telisotuzumab vedotin and showed an objective response rate (ORR) of 35% and duration of response (DOR) of 9.0 mo. Based on these

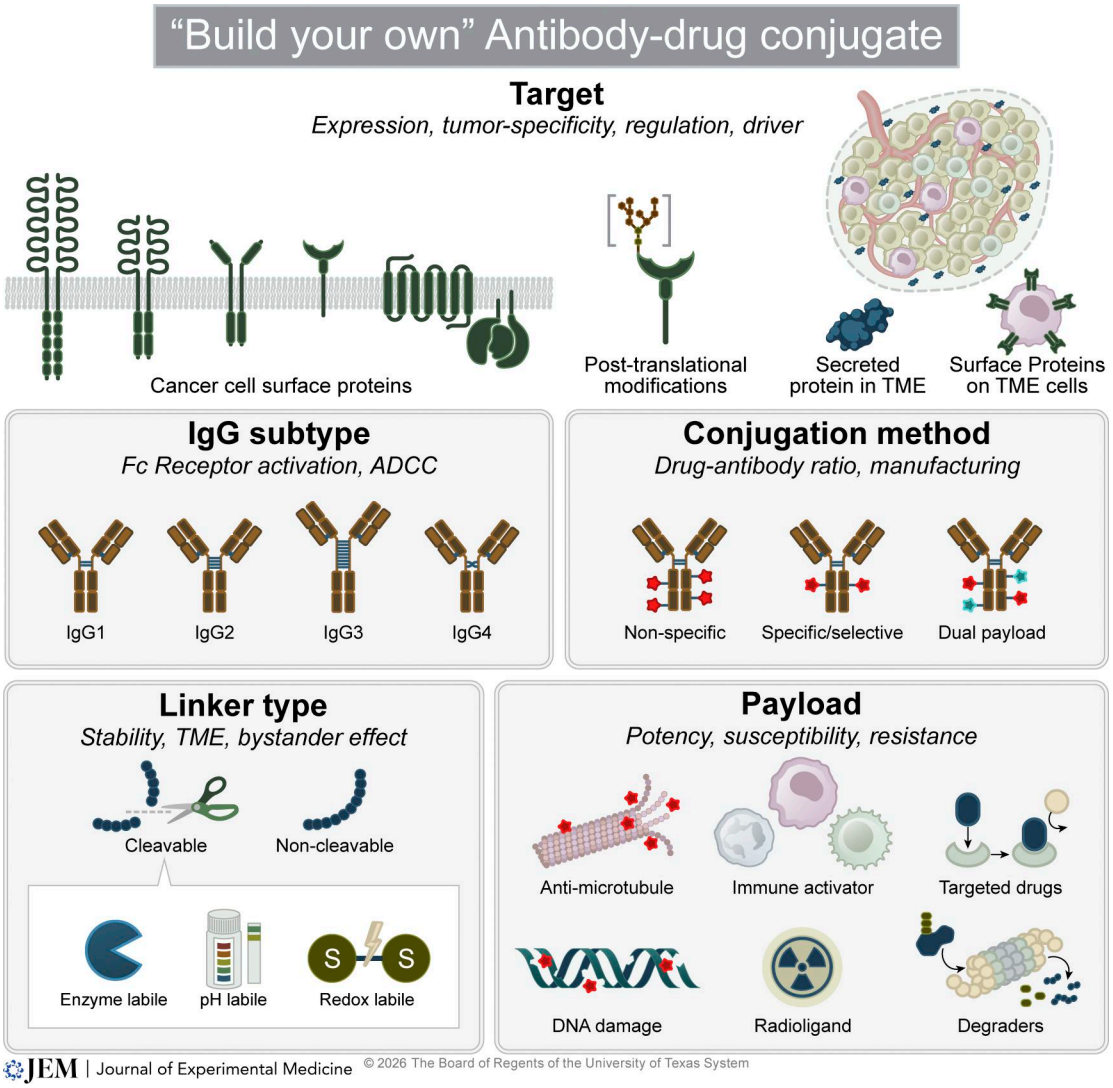

Figure 1. **ADC design menu.** Illustration highlighting the major components of ADC design used in currently approved and investigational ADCs: (1) target, (2) IgG subtype, (3) conjugation method, (4) linker, and (5) payload. Copyright used with the permission of The Board of Regents of the University of Texas System through The University of Texas MD Anderson Cancer Center.

results, telisotuzumab vedotin received accelerated FDA approval for this setting. The major adverse events observed were neuropathy and pneumonitis (Camidge et al., 2024).

Design of ADCs

Each component of the ADC is a crucial decision that determines important characteristics, including its target specificity, off-target toxicity, stability, therapeutic window, potency, bystander effect, and immune system activation (Fig. 1). Furthermore, even with the same target antibody, ADCs can have large differences in efficacy and indication as seen with T-DM1 and T-DXd. There are many lessons that can be learned from both the aforementioned clinical successes but also the many setbacks. Here, we describe each major component of an ADC, the general characteristics that have defined successful agents, competing interests that need to be balanced, and upcoming innovations. It is important to emphasize, however, that ADCs are complex therapeutic agents, and key determinants of pharmacokinetics, efficacy, and toxicity, are not fully understood.

Antibody

The first decision is to choose an ideal target to then generate an antibody against. Though most current ADC targets are found on the surface of cancer cells, therapies are emerging that target secreted proteins (Cela et al., 2025) or proteins found in the tumor-microenvironment (Storey et al., 2025; Gallant et al., 2024; Hooper et al., 2022). Ideal surface proteins are believed to have high expression, surface abundance, tumor-specificity, and turnover to promote internalization once the ADC is bound to its target. Though high cell surface density is desirable (Maecker et al., 2023), increased payload potency and bystander effect can allow for efficacy at lower thresholds (Akay et al., 2025). There is not a strict cutoff for normal tissue expression; however, on-target/off-tumor toxicity can often correlate with high expression found in alternative tissues such as HER2

expression in the heart (Pondé et al., 2016) and lungs (Liu et al., 2022) and TROP2 expression in the oral mucosa (Stepan et al., 2011). Multiple ADCs had to halt clinical development due to unexpectedly high rates of on-target/off-tumor effects such as severe skin toxicities with bivatuzumab mertansine, targeting CD44v6 (Riechelmann et al., 2008) that is expressed in the skin, and exudative gastritis with BR96-doxorubicin, targeting the Lewis Y antigen that is expressed in the GI tract (Gottlich et al., 2023). However, expression in a normal tissue does not always predict toxicity (Bosi et al., 2023), and many of the common toxicities seen reflect payload therapeutic class toxicities rather than ones specific for ADCs (i.e., neuropathy with microtubule inhibitors) (Nguyen et al., 2023). This is most apparent in the difference of toxicities between Dato-DXd and SG, two TROP2-targeting ADCs with TOP1i payloads. TROP2 is expressed in the salivary glands and mucosal tissues (Stepan et al., 2011), yet Dato-DXd causes much higher rates of stomatitis than SG. This may be due to the higher potency of DXd; other investigational TROP2 ADCs with higher potency payloads than SG also have higher rates of stomatitis (Meric-Bernstam et al., 2025). Furthermore, TROP2 is also not expressed in blood cells (Wang et al., 2025a), yet SG has very high rates of cytopenias. This is likely due to the relatively more unstable linker for SG leading to release of payload in circulation (Nguyen et al., 2023; Colombo et al., 2026). Expression of ADC targets in normal tissues clearly does not completely predict toxicities and is influenced by linker, payload, and tissue-intrinsic susceptibility to the payload. Nonetheless, most targets of successful ADCs have high expression in tumors and relatively low expression in majority of normal tissues.

Targets with important roles in tumorigenesis or survival may have advantages. The most clinically successful ADC, T-DXd, targets a well-known cancer driver in HER2 that was associated with a more aggressive disease with poor prognosis until the advent of HER2-targeting antibodies (Slamon et al., 1987). Many ADC targets have been associated with tumorigenesis and promoting cancer cell survival. There can also be therapeutic effect from disrupting function and downstream signaling of the target; there has been experimental evidence with HER2 (Nagata et al., 2004), TF (Breij et al., 2014), and MET (Wang et al., 2016). Selection of cancer drivers can also mitigate against clonal selection, which leads to antigen downregulation, loss, or mutation in resistance (Li et al., 2025; Chang et al., 2023).

Next is to decide on antibody design and binding affinity. Major characteristics to account for include target specificity, immunogenicity, and serum stability. Though, logically, it seems that higher affinity would be better, too high of an affinity can lead to unintended off-target effects. In preclinical models, MET-targeting ADCs with too high an affinity led to increased toxicity in the liver and other normal tissues, but decreased affinity had less off-target toxicity while maintaining therapeutic effect on cancer cells (Datta-Mannan et al., 2024). High affinity can also lead to concentration of the antibody at the vascular-tumor interface and reduced tumor penetration (Adams et al., 2001). This is known as the binding site barrier that can limit spatial penetration of the ADC (Wei et al., 2024). Initial ADCs used murine antibodies that led to immune reaction and limited efficacy before humanized constructs were made (Chari et al., 2014). There are also four human IgG subclasses (IgG1, IgG2, IgG3, and IgG4) that can be chosen to construct ADCs (Vidarsson et al., 2014; Yu et al., 2020). A potential determinant of immune effects of antibodies that include antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) is the binding affinity of the crystallizable fragment (Fc) of the antibody to the Fcγ receptors (FcγR) on immune effector cells. IgG3 and IgG1 have the highest complement activation and Fc-binding affinity (Yu et al., 2020; Chu et al., 2021). The majority of ADCs are constructed with IgG1 subclass antibodies. Though Fc interaction can promote ADCC, it can also lead to off-target toxicity through internalization through the Fc receptor in immune and other normal cells and also promote antibody sequestration. Antibody engineering and Fc modification can modulate the immune activation and off-target toxicities of these antibodies (Hoffmann et al., 2017; Moquist et al., 2024). Successful antibody development requires finding optimal binding affinity balancing target selectivity and tumor penetration and engineering to modulate immune effects.

Conjugation

An important parameter of ADCs is the DAR, which is the amount of payload that is attached to each antibody. Effective ADC design balances low potency of a low DAR with increased toxicity of a high DAR (Pettinato, 2021). The conjugation method used to attach the linker to the antibody is an important determination of the DAR and the distribution of the payload on the antibody molecule. The antibody–linker stability is also an important determinant of the pharmacokinetics of ADCs that is often overlooked; many currently approved ADCs will release the payload–linker complex from the antibody with a half-life of ∼7 days (Colombo et al., 2026). Interestingly, the majority of these payload–linker complexes end up attached to circulating albumin; the consequences of which have not been well studied (Colombo and Rich, 2022). There are two major categories of conjugation methods: nonspecific (or stochastic) and site specific. In nonspecific conjugation, the linker attachment can be to multiple sites on the antibody, and thus the exact site used and DAR can be variable. One of the most common methods that has been used on commercial antibodies is random lysine conjugation, where the linkers are attached to solvent-accessible lysine groups on the antibody. Early ADCs, such as gemtuzumab ozogamicin, using this conjugation technique had highly variable DARs that limited its therapeutic window (Joubert et al., 2020; Fan et al., 2025). However, with more modern manufacturing conditions, it has been shown that DAR can remain stable (Wu et al., 2019). Another example of this is using the four disulfide bonds found in IgG1 antibodies, one between each light and heavy chain pair and two between the heavy chains. The eight cysteines at these locations can be targeted for conjugation, but most current methods will lead to variability in which ones are conjugated between ADC molecules (Fu et al., 2022). However, newer ADCs such as T-DXd can have DARs that are almost 8, and thus, nearly every interchain cysteine is conjugated (Ogitani et al., 2016a). In site-specific conjugation, alternative methods introduce specific modifications to the antibody to then be able to control which site is being conjugated and have more precise control over the DAR.

Potential benefits include increasing ADC stability and homogeneity. This includes introducing specific cysteines, noncanonical amino acids, and modified glycans to then react with the linker (Walsh et al., 2021). The full spectrum of conjugation technologies is reviewed elsewhere (Matsuda et al., 2025; Fan et al., 2025). Novel methodologies also allow development of ADCs with dual payloads (Zhou et al., 2024b; Wen et al., 2025). Though site-specific ADCs have shown better preclinical parameters and offer more precise tuning of DAR, clinical evidence of their advantage is yet to be fully established (Fan et al., 2025).

Linker

The linker that connects the payload to the conjugation site also has important properties that determine stability, cleavability, therapeutic index, and bystander effects from the ADC. It is important to separate linker stability from linker cleavability. Linker stability refers to premature release of payload regardless of environment. Cleavability, on the other hand, is a feature; the linker being designed to release the payload based on presence of a trigger in the tumor microenvironment or target cancer cell. Initial ADCs were limited by unstable linkers that led to premature release in the plasma and systemic toxicity (Chari et al., 2014; Ducry and Stump, 2010). However, increasing stability does not necessarily mean universal less toxicity or more efficacy. A recently published insightful review discusses the balance of linker stability; unstable linkers lead to premature payload release, but high stability can also increase certain toxicities; with MMAE ADCs, higher stability of the linker is associated with increased corneal toxicity (Colombo et al., 2026). Cantuzumab mertansine (Helft et al., 2004) and DCDS0780A (Herrera et al., 2022) are two examples of unsuccessful ADCs designed with more stable linkers that ultimately displayed high rates of corneal events. Preclinical testing of increasingly stable linkers has shown that intermediate stability having the optimal efficacy; not the most stable construct (Kellogg et al., 2011; Su and Zhang, 2021). This is confounded by the fact that when linkers are more stable, they also may be more difficult to cleave in the TME, lowering the concentration of payload in the tumor. All but one FDA-approved ADC for solid tumors have cleavable linkers. One example is linkers susceptible to cathepsins, a family of proteases that can play a role in tumor invasion through breakdown of the extracellular matrix (Yadati et al., 2020). Cathepsin B and cathepsin L are highly expressed in multiple tumor types and are believed to contribute to ADC linker cleavage (Liu et al., 2024; Sudhan and Siemann, 2015; Tsao et al., 2025). Another example is acid-labile linkers sensitive to the low pH found in the tumor microenvironment (Hosonuma and Yoshimura, 2023) and in lysosomes (Yim and Mizushima, 2020). Linkers can also be susceptible to redox, oftentimes having a disulfide bond that is susceptible to high glutathione concentrations intracellularly (Franco and Cidlowski, 2009). Non-cleavable linkers are made to be stable and can prevent premature release of the payload before the ADC is broken down internally within the lysosome of the cell. T-DM1 is an example of an ADC with a non-cleavable linker (Peddi and Hurvitz, 2013). Advantages include greater plasma stability and lower off-target activity. However, this also comes at a tradeoff with efficacy (Ogitani et al., 2016b). When T-DM1 is broken down, the payload and linker remain attached, and this complex is not membrane permeable. Thus, there is no "bystander effect," where the payload can permeate to nearby cells that may not have high expression of the target (Ogitani et al., 2016b). There are many other linker design considerations, including the addition of spacers to help optimize flexibility, length, and hydrophobicity (Matsuda et al., 2025; Lei et al., 2025; Su et al., 2021). Most successful ADCs have intermediately stable and cleavable linkers, and additional study of tumor-specific TME characteristics may help expand ADC efficacy to tumors with low target expression.

Payload

The final component of the ADC is the payload, and this is classically a cytotoxic agent. There are two main classes of drugs in currently approved ADCs for solid tumors: topoisomerase 1 inhibitors and anti-microtubule agents. The majority of topoisomerase I inhibitor systemic therapies and payloads are derivatives of camptothecin, an alkaloid found in plants. Examples include SN-38, exatecan, and DXd. Anti-microtubule payloads include DM1, DM4, MMAE, and monomethyl auristatin F. There are many important considerations when choosing and deciding on a payload. First is balancing on-target killing and off-target toxicity. A key advantage of precision delivery of ADCs is the ability to conjugate agents with high potency. Early studies with systemic exatecan showed promising activity but a limited therapeutic window due to bone marrow toxicity that prevented its development into systemic therapy (Ajani et al., 2005). However, DXd, a payload derived from exatecan, has been successfully incorporated into multiple ADCs with an improved therapeutic window (Modi et al., 2020, 2022; Bardia et al., 2024a; Ahn et al., 2025). Potency also has been balanced; pyrrolobenzodiazepine dimers are highly cytotoxic, but many ADCs with pyrrolobenzodiazepine (PBD) payloads have been discontinued due to high toxicities (Hartley, 2021). Membrane permeability of the payload can also determine the bystander effect. When DM1 is released from T-DM1, it is polar and thus does not diffuse into neighboring cells that limits this effect (Ogitani et al., 2016b). Previous treatment lines and development of cross-resistance is also an important consideration. Multiple studies in breast cancer have shown that PFS is generally lower with a second ADC with the same payload class (Huppert et al., 2025; Nezirevic et al., 2025). Given the predominance of topoisomerase I inhibitor and anti-microtubule agents in current ADC development (Colombo et al., 2024), diversification of payloads will likely be important for ADC efficacy in pretreated patients (Su et al., 2021). Many novel payloads that include DNA-damage toxins (Calabretta et al., 2022), RNA toxins (Orlik et al., 2022; Pahl et al., 2018), radioisotopes (Lawal et al., 2025), protein degraders (Nakazawa et al., 2024), and immune modulators (Sega et al., 2025; Li et al., 2023) have been developed and are being tested in early-phase trials.

Determinants of ADC efficacy

ADCs have received FDA approval across various indications in solid tumors and have led to impressive improvements in

outcomes in various cancer types. However, the efficacy is not universal, and patient tumors can have inherent resistance or acquired resistance. Here, we discuss the current understanding of ADC efficacy and resistance.

Expression and histology

Given that ADC binding and internalization is thought to be essential for its therapeutic mechanism, expression of the target would presumably be an important determinant of efficacy. However, there is not always a clear relationship between expression levels and clinical outcome. For example, in breast cancer, T-DXd has shown efficacy and is approved across a wide range of expression, from ultralow staining to IHC 3^+-positive staining. In addition, in the phase 2 DAISY trial, responses were seen in patients with no detectable HER2 expression (29.7%) (Mosele et al., 2023). Intriguingly, recent studies indicate that extracellular proteases in the tumor microenvironment can lead to release of the DXd payload (Tsao et al., 2025). The tumor microenvironment is also acidic, and ADCs with acid-labile linkers, such as SG, could also have payload release without internalization (Tolaney et al., 2025b). On the other hand, many approvals of ADCs do not require checking for expression that includes SG, Dato-DXd, EV, and tisotumab vedotin. Studies evaluating relationship between expression of TROP2 determined by both RNA levels and IHC staining have not shown conclusive relationship to clinical outcomes with SG in TNBC (Bardia et al., 2021b) or $HR^+/HER2^-$ breast cancer (Bardia et al., 2023), though higher expression does have a positive trend with improved outcomes (Bardia et al., 2021b). The phase 2 ADC-MATCH trial is assessing if patients with solid tumor that have high expression of HER2, NECTIN4, or TROP2 will benefit from matched ADC therapies regardless of histology (NCI10397). The discrepancy between expression and efficacy suggests our current tools, relying mostly on IHC of a single sample, may not be accurately quantifying heterogeneous expression (Dernbach et al., 2025; Wang et al., 2024) across all tumor sites or that target-independent mechanisms of efficacy, such as payload sensitivity and extracellular payload release, may be playing an unappreciated role in clinical outcomes that need further study.

Mechanisms of inherent and acquired resistance

Patient tumors can harbor inherent resistance to ADCs, leading to limited upfront efficacy, or they can develop resistance that eventually can lead to progression. There are five major steps to the therapeutic activity of ADCs, and at each one there can be factors that limit efficacy: (1) antigen binding, (2) internalization, (3) lysosomal degradation, (4) payload release and transport, and (5) payload cytotoxic activity.

The first step in ADC activity is binding to the target on the surface of cancer cells. As discussed previously, expression and clinical activity do not always correlate, but in general, a trend toward improved activity with higher expression is observed. Lower expressing tumors or those with heterogeneity in expression may harbor inherent resistance to ADCs. For example, in a study of neoadjuvant therapy with T-DM1 with pertuzumab, expression heterogeneity in tumor samples was associated with lower rates of response (Filho et al., 2021). During treatment, expression of the target can decrease or be lost. For example, a study of 34 patients treated with T-DXd with pre-posttreatment biopsies showed that 34% had HER2 loss, and 29.4% of patients had HER2 score decrease. An additional study showed HER2 loss in 52% (26/50) patients treated with T-DXd (Chen et al., 2025). Mutations on the binding surface of the target can also occur that lead to decreased binding as has been seen with HER2 (Chen et al., 2025). Antigen-specific mechanisms of resistance may be mitigated with newer ADCs that have bystander effect as well as bispecific ADCs that bind to multiple targets on the cell surface (Gu et al., 2024).

The next essential step is internalization of the ADC–antigen complex. This can be done through various endocytic pathways that include clathrin-mediated and clathrin-independent; the latter includes many alternative pathways, including caveolin-mediated endocytosis (Rennick et al., 2021). Antigens differ in the pathways used for internalization; for example, it is believed that HER2 is internalized with both clathrin-mediated and caveolin-mediated endocytosis (Hammood et al., 2021). Alterations in these pathways could lead to resistance. For example, endophilin A2 (also named SH3GL1), a protein that is important for clathrin-independent internalization (Renard et al., 2015), promotes internalization of HER2 (Baldassarre et al., 2017). Silencing its expression in cell lines leads to impaired internalization and resistance to HER2 antibody-based therapies (Baldassarre et al., 2017). Preclinical studies have also suggested that increased expression of caveolin-1 is associated with decreased sensitivity to HER2-directed therapies in gastric cancer (Pereira et al., 2022); however, in breast cancer cell lines, increased caveolin-1 expression was associated with increased sensitivity (Chung et al., 2015). In addition, clear evidence of changes in the endocytosis machinery happening in ADC-resistant patient tumors has yet to be reported. Overall, additional research is needed to establish resistance mechanisms affecting ADC-target internalization and develop strategies for enhanced internalization.

Once internalized, ADCs are typically trafficked to the acidic environment of the lysosome, where they are degraded, and the linker is cleaved to release the payload. The acidic environment of the lysosome is essential for the proper function of its protease enzymes used to cleave enzyme-cleavable linker. The low pH is also important for acid-labile linkers. In breast cancer and gastric cancer cell lines with induced T-DM1 resistance, lysosomal alkalization and impaired enzyme activity has been observed (Ríos-Luci et al., 2017; Wang et al., 2017a). In addition, inhibiting acidification of lysosomes in gastric cell lines has been shown to reduce T-DM1 activity in gastric cancer (Wang et al., 2017a). Thus, lysosomal dysfunction could be a mechanism to develop ADC resistance, though a therapeutic target to reverse this dysfunction has not been established.

A key aspect of the function of both topoisomerase-1 inhibitors and microtubule disrupters is transport from the lysosome to their site of activity in the nucleus and cytoplasm, respectively. For ADCs with payloads that are not cleavable, transport of the payload out of the lysosome is an essential step. A study found that SLC46A3 was essential for transport of the catabolites of T-DM1 into the cytoplasm, and its silencing

increased the concentration of catabolites in the lysosome (Hamblett et al., 2015). Further study in in vitro and in vivo models with acquired T-DM1 resistance showed that diminished SLC46A3 expression could also be a mechanism of acquired resistance (Kinneer et al., 2018). In addition, expression of multiple efflux transporters of the ATP-binding cassette class has been shown to correlate with outcomes and be a mechanisms of resistance to ADCs. Examples include MDR1 or P-gp (encoded by *ABCB1*), MRP1 (encoded by *ABCC1*), MRP2 (encoded by *ABCC2*), and BCRP (encoded by *ABCG2*). Studies of cell lines with acquired T-DM1 resistance revealed increased ABCC1 expression as a common mechanism (Loganzo et al., 2015; Li et al., 2018). Recent large-scale transcriptomic efforts have also revealed trends toward higher expression of MDR1, MRP1, and BCRP in patients with acquired resistance to ADCs (Alkassis et al., 2025; Sledge et al., 2025). In addition, high expression of MDR1 was associated with shorter duration of treatment and OS with T-DXd treatment in breast cancer patients (Alkassis et al., 2025). Choosing payloads with membrane permeability, bystander effect, and poor substrates for efflux transporters can help mitigate this effect (Roth et al., 2026).

The final step is the effect of the payload, and currently, this consists of either a topoisomerase 1 inhibitor or an anti-microtubule agent, and there can be development of resistance to the cytotoxic effect of the payload. In multiple studies of ADCs, samples at progression have shown development of alterations in the TOP1 gene that may confer resistance to the TOP1i payload (Shitara et al., 2024; Abelman et al., 2025; Coates et al., 2021). In a study of breast cancer patients treated with TOP1i ADCs and with pre- and post-progression ctDNA analysis, 12.9% of patients were found to have TOP1 mutations and had poor outcomes with subsequent ADCs with TOP1i payloads (Abelman et al., 2025). Though alterations in expression of tubulin proteins and mutations have been explored as mechanisms of resistance to systemic anti-microtubule agents such as taxanes (Mozzetti et al., 2005; Uba et al., 2023; Maloney et al., 2020), their exact role in conferring resistance to ADC payloads has not been established. However, resistant cells have been shown to avoid cell death in preclinical breast cancer models treated with T-DM1 by having defective cyclin B1 that plays an important role in mitotic catastrophe (Sabbaghi et al., 2017). Multiple resistance mechanisms can also develop in tumors from the same patient (Coates et al., 2021). New strategies conjugating multiple payloads on the same ADC are being developed to help overcome resistance (Khosravifarsani et al., 2025).

Combination therapies with ADCs

Though ADCs have shown potent activity as single agents, virtually all patients with widely metastatic solid tumors will eventually progress. ADCs often have a favorable therapeutic window and toxicity profile that could make them favorable for combination therapies. Rational combinations that synergize with ADCs could improve clinical outcomes. Currently, EV plus pembrolizumab is the only approved ADC combination for solid tumors; however, there are many promising ADC combination therapies with strong preclinical and clinical data that are being developed. We categorize them based on their role in the pathway of ADC efficacy (Fig. 2).

Regulation of surface target

Many therapeutic agents modulate the expression of ADC targets. In breast cancer, our group has shown that treatment with decitabine, a DNA methyltransferase inhibitor, can lead to upregulation and increased expression of TROP2 (Zhao et al., 2023). SG and decitabine show in vitro synergy (Zhao et al., 2023). In addition, we also observed that decitabine increases the expression of SLFN11. SLFN11 is a DNA/RNA helicase, and its expression is often correlated with sensitivity to therapies such as TOP1i (Murai et al., 2019; Metzner et al., 2022). Valemetostat, an EZH1/EZH2 inhibitor, has also been shown to increase the expression of HER2 and SLFN11 and enhance the antitumor activities of T-DXd and Dato-DXd (Honma et al., 2025). There is an ongoing trial assessing these combinations (NCT06244485). There has also been evidence that statin therapy can increase HER2 density on the cancer cell surface (Rao et al., 2023).

Target internalization

Therapies can also enhance the internalization of the ADC target. This has been most consistently seen with the irreversible pan-HER2 inhibitor neratinib. Preclinical studies showed that neratinib treatment led to increased ubiquitination and internalization of HER2, and this also led to increased T-DM1 internalization and efficacy in lung cancer cell lines and PDX models (Li et al., 2020a). This was also seen in gastric cancer models (Zidel et al., 2025). The phase 2 Translational Breast Cancer Research Consortium trial tested the combination of neratinib and T-DM1 in HER2$^+$ breast cancer patients with brain metastasis and showed promising intracranial activity of the combination even in setting of previous T-DM1 exposure (Freedman et al., 2024). A phase I trial testing the combination of T-DXd and neratinib in solid tumors with HER2 IHC 3$^+$. HER2 amplification or HER2-activating mutations showed responses in pancreatic, gastroesophageal, and ovarian cancer during dose escalation (Davis et al., 2025).

DNA damage response (DDR) pathway inhibitor

For ADCs with TOP1i payloads, combination with inhibitors of the DDR pathway inhibitors can be synergistic and lead to synthetic lethality. The TOP1 enzyme recognizes supercoiled DNA and creates a single-strand break, unwinds the DNA, and then repairs the single-strand break. TOP1 inhibitors trap the TOP1 after it creates the single-strand break, and this is known as a TOP1 cleavage complex (TOP1cc). This leads to accumulation of TOP1cc's and single-strand breaks (Pommier, 2006). Poly (ADP-ribose) polymerases (PARPs) are critical components to multiple DNA repair processes. PARPs play an important role in recognition of early DNA lesions, including the TOP1cc to regulate repair (Chowdhuri and Das, 2021). PARP inhibitors (PARPi) have shown synergy with TOP1 inhibitors, including topotecan in preclinical models (Smith et al., 2005; Znojek et al., 2014). Furthermore, PARPi enhance the cytotoxicity of SN-38, the payload of SG (Tahara et al., 2014). Multiple trials have tested the combination of ADC and PARPi, which was initially limited by

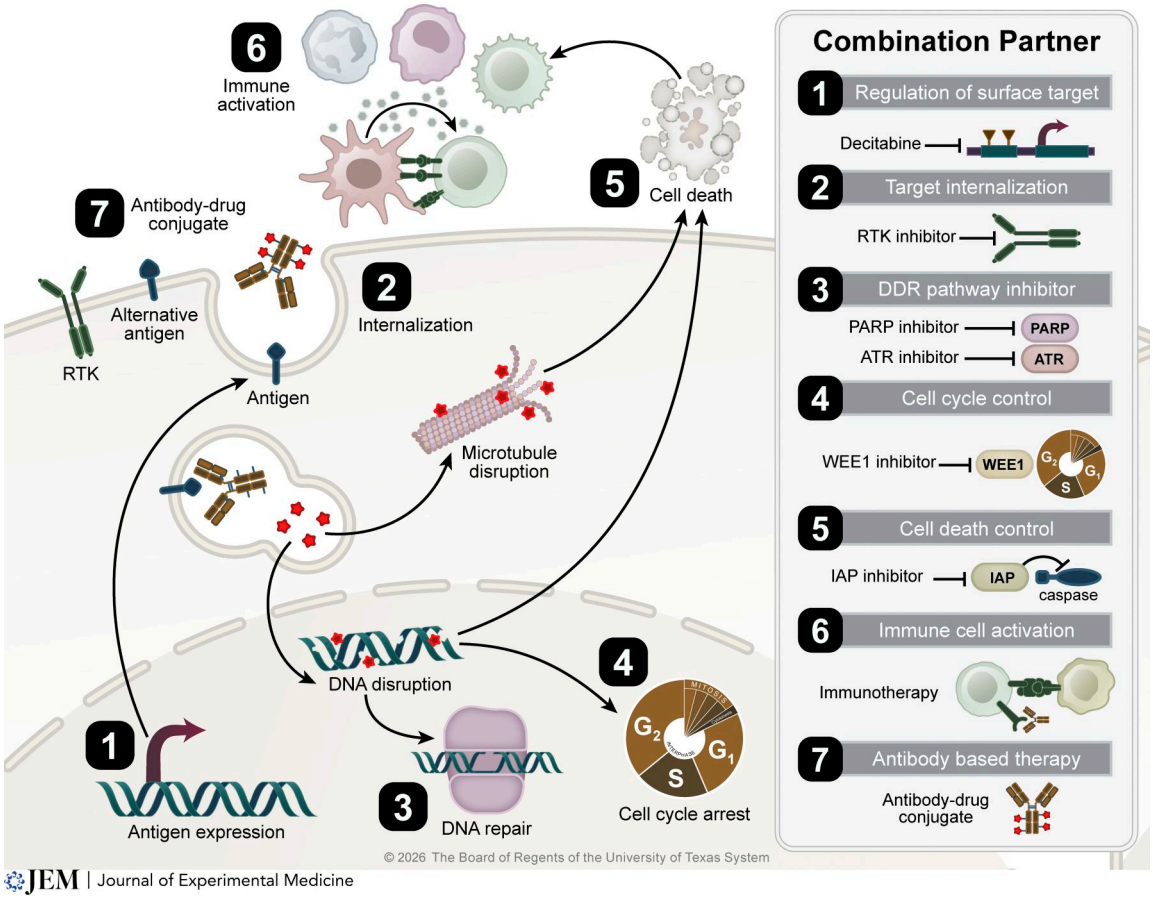

Figure 2. **ADC combination therapies.** Illustration highlighting seven categories of ADC combination therapies that are currently being developed. Copyright used with the permission of The Board of Regents of the University of Texas System through The University of Texas MD Anderson Cancer Center.

toxicity. To overcome toxicity, Bardia et al. tested sequential dosing of SG and PARPi in TNBC preclinical models, and the combination showed synergy in enhancing the efficacy of SG. These data were used to rationalize a phase I trial with SG and talazoparib, where sequential dosing had better PFS and safety than concurrent administration (Bardia et al., 2024c). A subsequent phase 2 trial of SG and talazoparib in patients with TNBC showed an ORR of 30.1% (Abelman et al., 2024). Furthermore, accumulation of TOP1cc also increases replication stress. An important mediator of response to replication stress is the ataxia telangiectasia and Rad3-related protein (ATR). ATR helps to coordinate repair while also leading to cell cycle arrest. Inhibition of ATR in addition to TOP1i can lead to progression of the cell cycle in the presence of DNA damage that can lead to mitotic catastrophe and cell death (Cliby et al., 2002). A siRNA screen of nearly 7,000 genes in a breast cancer cell line for synthetic lethality with the TOP1i camptothecin identified ATR as a top candidate (Jossé et al., 2014). The combination of T-DXd and the ATR inhibitor, ceralasertib, showed promising efficacy in the phase I DASH trial with ORR of 57% in HER2 3^+ metastatic solid tumors and ORR of 27% in HER2 $1^+/2^+$ metastatic solid tumors (Raghav et al., 2025). In a phase I trial of SG with the ATR inhibitor, berzosertib, in solid tumors, there were no dose-limiting toxicities or clinically relevant adverse events and responses were seen in 2/12 patients (Abel et al., 2023). Combination of ATRi and Dato-DXd has also been shown to resensitize gastric cell lines with acquired resistance to Dato-DXd (Przybyla et al., 2023).

Cell cycle control

A key step in effective DNA-damage repair, especially after treatment with DNA-damaging agents, is cell cycle arrest. Wee1 is an important cell cycle checkpoint that regulates the transition from G2 to mitosis. When there is DNA damage, Wee1 leads to cell cycle arrest that allows time for DNA repair (Thangaretnam et al., 2025). Inhibition of Wee1 has been shown to prematurely force cells into mitosis leading to abnormal mitosis and ultimately cell death (Aarts et al., 2012). Preclinical testing has shown single-agent efficacy of Wee1 inhibitors such as azenosertib (Ma et al., 2025; Huang et al., 2021) and adavosertib (Vuaroqueaux et al., 2022) across a wide range of tumor types. A key mediator of sensitivity to Wee1 inhibition has been shown to be amplification of cyclin E1 (*CCNE1*). CCNE1 regulates G1 to S transition, and amplification is associated with worse prognosis and increased replication stress. Adavosertib has shown promising single agent activity in early-phase trials in uterine serous

carcinoma (Liu et al., 2025a) and *CCNE1*-amplified solid tumors (Fu et al., 2023). *CCNE1* amplification can also mediate resistance to HER2-directed therapies, and *CCNE1* and *HER2* coamplification is common (DiPeri et al., 2023). DiPeri et al. showed that *CCNE1* amplification can also decrease sensitivity to T-DXd. Combination treatment of T-DXd plus adavosertib had synergy in both HER2 low (IHC $1^+/2^+$) and HER2 high (IHC 3^+) tumors in PDX model experiments (DiPeri et al., 2023). Cell line experiments have also shown synergy between both TOP1i and ADCs with TOP1i payloads and Wee1 inhibitors (Ma et al., 2024). There are ongoing trials testing ADC and Wee1 inhibitor combinations (Doerfler et al., 2025).

Cell death control

Inhibitors of apoptosis proteins (IAPs) play an important role in regulating apoptosis. They can prevent programmed cell death and are overexpressed in many cancer types (Ye et al., 2025). IAPs have been shown to confer drug resistance to various chemotherapeutic agents (Ye et al., 2025). FL118 is a camptothecin analog that has also been shown to inhibit expression of IAPs (Ling et al., 2015). It has shown efficacy in topotecan- and irinotecan-resistant cell lines (Ling et al., 2015). Given these findings, further research is warranted to assess the combination of IAP inhibitors and TOP1i ADCs.

Immune cell activation

The interplay between ADCs and the immune system plays an important role in their efficacy, and many effective combinations of ADCs and checkpoint inhibitor therapies have been developed. Potent cytotoxic payloads of ADCs can lead to immunogenic cell death (Schulte et al., 2025; Iwata et al., 2018; Müller et al., 2014). Upon ADC-mediated cytotoxicity, cancer cells release damage-associated molecular patterns into the TME, which are recognized by immature dendritic cells (DCs) via toll-like receptors. This interaction, along with direct stimulation exerted by the payload, boosts the maturation of DCs that migrate in lymph nodes to activate naïve T cells (Fuentes-Antrás et al., 2023). Activated CD8 T cells can subsequently infiltrate the tumor and lead to increased cytotoxicity (Iwata et al., 2018). In addition, ADCs can activate the immune system through ADCC, ADCP, and complement-dependent cellular cytotoxicity (Chang et al., 2023). As described above, the combination of EV and pembrolizumab has been approved in metastatic urothelial cancer, and many additional ADC plus immunotherapy combinations have shown promising results. As first-line therapy for patients with metastatic TNBC, SG plus pembrolizumab displayed superior PFS (HR-0.65), DOR (16.5 vs. 9.2 mo), and a trend toward improved OS (immature) when compared with chemotherapy plus pembrolizumab in the phase 3 ASCENT-04 trial (Tolaney et al., 2025a). In the cohort of metastatic TNBC patients treated with first-line Dato-DXd in combination with durvalumab in the BEGONIA trial, the confirmed ORR was 79% and the response was irrespective of PD-L1 expression; 87% of patients had tumors with low PD-L1 expression. Median PFS was 13.8 mo (Schmid et al., 2023). There are multiple ongoing trials assessing ADC and immunotherapy combinations.

Antibody therapy combinations

Cancer cells can display multiple cell surface targets, and this can allow for ADC combination therapies with other antibody-based therapies and ADCs. For example, there is significant co-expression of TROP2 and NECTIN4 in metastatic urothelial cancer (Fan et al., 2022). The phase I double-antibody–drug trial of SG plus EV showed promising results, indicating that ADCs can be used in combination. For patients with metastatic urothelial cancer, the response rate was 70% across the dose ranges in the trial, but there was significant toxicity with 48% of patients requiring dose reductions and occurrence of one grade 5 toxicity (McGregor et al., 2024). The recently approved combination of T-DXd and pertuzumab shows combining ADC with antibody targeting a different target domain can be successful (Tolaney et al., 2026). In addition, ADCs with unique payloads may have favorable toxicity profiles to allow for more successful ADC combination therapies. Finally, bispecific ADCs that target multiple cell surface receptors are also in clinical development. They can be engineered to only have potent activity when expression of both antigens is high, and this significantly limit off-target effects (Luo et al., 2025). Overall, there are many innovations in ADC design that may lead to effective ADC combinations in the future.

Conclusions

With the pace of current research and innovation, ADCs are poised to enter the therapeutic toolkit for a wide range of tumor types. There are over 400 ADCs currently in development globally (Wang et al., 2025b), and in 2024 alone, there were over 100 first-in-human trials of ADCs (Crescioli and Reichert, 2025). Though they hold great promise, there are many limitations that need to be considered. There are many resistance mechanisms, both inherent and acquired, that can limit their efficacy. Furthermore, lack of payload diversity and cross-resistance may greatly dampen the possibility of sequential ADC therapy. ADCs also have significant toxicities that need to be considered (Cheng et al., 2025). As use of ADCs spreads, it will be important to educate clinicians on recognizing and managing these toxicities. Even with these limitations, the numerous innovations in ADC design and potential combination partners offer hope for greater efficacy and improved patient outcomes in the future.

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