Mechanism of Action, Clinical Applications, and Drug Resistance Challenges of HER2-Targeted Antibody-Drug Conjugates

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Abstract

Amplification, overexpression, and activating mutations of human epidermal growth factor receptor 2 (HER2) are key oncogenic drivers in multiple solid tumors. Antibody–drug conjugates (ADCs) have reshaped the treatment paradigm for HER2-altered tumors by integrating the targeting specificity of monoclonal antibodies with the potent cytotoxicity of small-molecule cytotoxins. This review systematically summarizes the molecular design and mechanisms of action of HER2-targeted ADCs, pivotal clinical evidence for approved agents, innovative strategies for next-generation ADCs, expansion across tumor types, toxicity profiles and comprehensive management, resistance mechanisms, and the exploration of combination therapies. It further provides an in-depth discussion of the bottlenecks in clinical translation, including companion diagnostics, HER2 heterogeneity, and the standardization of testing. Drawing on the development experience of TROP2-targeted ADCs, this article also envisions future directions such as bispecific ADCs, immune synergies, local drug delivery, and sequential therapy combining ADCs with small-molecule inhibitors, aiming to provide a comprehensive framework for the precision treatment of HER2-altered solid tumors.

Key words

HER2, Antibody-drug conjugate, Breast cancer, Non-small cell lung cancer,Drug resistance

1. Introduction

Human epidermal growth factor receptor 2 (HER2) is a member of the ErbB/HER family of receptor tyrosine kinases. Amplification or overexpression of its encoding gene, ERBB2, is detected in approximately 20%–30% of breast cancers and can act as a driver event, constitutively activating downstream pro-proliferative and anti-apoptotic signaling cascades, such as the phosphatidylinositol 3-kinase (PI3K)/AKT and mitogen-activated protein kinase (MAPK) pathways. Consequently, HER2 alterations are closely associated with more aggressive biological behavior, poor prognosis, and shorter overall survival. Currently, the standard neoadjuvant and adjuvant treatment for HER2-positive breast cancer is based on chemotherapy combined with HER2-targeted monoclonal antibodies, such as trastuzumab and pertuzumab, achieving synergistic antitumor effects through dual blockade of receptor dimerization and both ligand-dependent and ligand-independent signaling. Against this backdrop, HER2-targeted antibody–drug conjugates (ADCs) have demonstrated transformative efficacy across multiple HER2-expressing solid tumors. Their core design integrates the precise targeting capability of a monoclonal antibody with a highly potent cytotoxic payload via a linker, thereby achieving selective killing of tumor cells. The clinical activity of ADCs is governed

by a complex interplay of factors, including not only the expression level and internalization efficiency of the target antigen, but also antibody affinity and epitope selection, linker stability and cleavage mechanism (cleavable versus non-cleavable), the payload's mechanism of action and toxicity profile, as well as critical physicochemical properties such as the drug-to-antibody ratio (DAR). Among these agents, ado-trastuzumab emtansine (T-DM1), the first ADC approved for solid tumors, employs a non-cleavable thioether linker to carry the microtubule inhibitor DM1. In contrast, the next-generation ADC trastuzumab deruxtecan (T-DXd) utilizes an enzyme-cleavable tetrapeptide linker conjugated to the topoisomerase I inhibitor DXd. With its high drug-to-antibody ratio of approximately 8 and a distinctive bystander effect, T-DXd is effective not only against tumors with high HER2 expression, but also demonstrates clinical benefit in HER2-low and even heterogeneous lesions, thereby reshaping the traditional therapeutic boundaries of breast cancer. However, with expanding clinical use, acquired resistance to T-DM1 and T-DXd has gradually emerged. The underlying mechanisms involve loss or downregulation of the HER2 antigen, overexpression of drug efflux pumps such as P-glycoprotein, premature linker cleavage, payload inactivation, as well as reactivation of the PI3K/AKT pathway and dysregulation of apoptotic signaling pathways. To address this challenge, novel combination regimens based on resistance mechanisms are being actively explored, such as combinations with immune checkpoint inhibitors, tyrosine kinase inhibitors, or DNA damage repair pathway inhibitors, along with sequential ADC strategies that target different antigens or employ different payloads. Furthermore, bispecific and biparatopic ADCs, next-generation ADCs carrying novel payloads such as RNA polymerase inhibitors or immune agonists, and precision engineering approaches including site-specific conjugation technology are rapidly advancing the field toward greater precision and reduced systemic toxicity.

2. Research Progress of Antibody–Drug Conjugates (ADCs) in the Treatment of Breast Cancer and Solid Tumors: From HER2 to TROP2

Antibody–drug conjugates (ADCs) represent one of the most groundbreaking advances in the field of targeted cancer therapy in recent years. The core design concept lies in integrating the high targeting specificity of monoclonal antibodies with the potent cytotoxicity of small-molecule chemotherapeutic drugs. Through the precise recognition of tumor surface antigens by the antibody, the payload is selectively delivered into cancer cells, thereby enhancing antitumor efficacy while substantially reducing toxic side effects on normal tissues. This "precision-guided" strategy has achieved remarkable success in a variety of solid tumors and hematologic malignancies. Among the targets, HER2 and TROP2 stand out as two of the most representative, leading the evolution of ADCs from "classic targeting" to "pan-tumor coverage."

The advent of ADCs has fundamentally altered this landscape. As of 2022, two HER2-targeted ADCs had received FDA approval for the second-line treatment of HER2-positive breast cancer. The first is ado-trastuzumab emtansine (T-DM1, Kadcyla®), which employs trastuzumab as the carrier to deliver the microtubule inhibitor DM1, and is the first ADC approved for solid tumors. The second is fam-trastuzumab deruxtecan-nxki (T-DXd, Enhertu®), which also uses trastuzumab as the antibody backbone but is armed with the topoisomerase I inhibitor DXd. The latter represents a major technological leap for next-generation ADCs: the DXd payload is membrane-permeable, enabling it not only to kill targeted HER2-overexpressing cancer cells but also to diffuse into the surrounding tumor microenvironment after target cell death, thereby exerting a "bystander effect" that efficiently eradicates adjacent HER2-negative or HER2-low tumor cells and overcomes the therapeutic bottleneck imposed by tumor heterogeneity. The DESTINY-Breast03 clinical trial further demonstrated that, in patients with HER2-positive metastatic breast cancer who had progressed on prior first-line therapy, second-line T-DXd yielded significantly superior overall survival compared with T-DM1, establishing its position as a new standard of care. Nevertheless, HER2-targeted ADCs still face considerable challenges, including complex resistance mechanisms such as downregulation of target antigen expression, reduced payload sensitivity, and overexpression of drug efflux pumps, as well as variations in efficacy caused by heterogeneous intratumoral ADC distribution. Although novel ADCs with a bystander effect can partially overcome resistance to T-DM1, data on sequential strategies and cross-resistance between different ADCs remain extremely limited and warrant further investigation [1].

Meanwhile, the target spectrum of ADCs is expanding from HER2, a marker confined to a single cancer type and a subset of patients, toward more broadly applicable target antigens, among which the discovery of TROP2 has attracted particular attention. TROP2 (trophoblast cell surface antigen 2) is a transmembrane glycoprotein initially identified in trophoblast cells; it was subsequently found to be highly expressed in a wide variety of solid cancers while exhibiting low expression levels in normal tissues. This differential expression pat-

tern renders it a highly promising "pan-cancer" ADC target. To date, two TROP2-targeted ADCs have entered clinical development and demonstrated promising potential. The first is sacituzumab govitecan (SG, Trodelvy®), which consists of the humanized anti-TROP2 monoclonal antibody hRS7 conjugated via a hydrolyzable linker to approximately eight molecules of SN-38, the active metabolite of irinotecan and a potent topoisomerase I inhibitor. Upon internalization, SN-38 is released, inducing DNA damage and apoptosis; SG is currently approved for triple-negative breast cancer and urothelial carcinoma. The second is datopotamab deruxtecan (Dato-DXd), which employs a more stable linker to conjugate the topoisomerase I inhibitor deruxtecan, enabling more selective delivery of the payload to tumor sites. Encouraging efficacy has also been observed in recurrent endometrial cancer and ovarian cancer. Although TROP2 ADCs have broadened the patient population that can benefit, their development still faces considerable bottlenecks: TROP2 expression levels assessed by immunohistochemistry cannot reliably predict therapeutic efficacy, and effective companion diagnostic biomarkers remain lacking; furthermore, target protein alterations, payload resistance, and compensatory activation of downstream signaling pathways such as PI3K/AKT, ERK-MAPK, and JAK-STAT can all mediate acquired drug resistance, limiting the long-term effectiveness of treatment [2].

Reflecting on the development trajectories of these two major targets, ADC technology is rapidly evolving from the first generation (exemplified by T-DM1) to the second generation (exemplified by T-DXd and SG) and onward to even more sophisticated platforms. The core breakthroughs reside in the innovation of payload types—shifting from microtubule inhibitors to topoisomerase I inhibitors—coupled with meticulous optimization of linker design and the drug-to-antibody ratio (DAR). In particular, the introduction of the “bystander effect” has empowered ADCs not only to address tumor heterogeneity but also to extend indications to previously difficult-to-treat populations, such as those with HER2-low expression. Future research directions will focus on: developing reliable predictive biomarkers to guide precise patient selection; exploring combination strategies that pair ADCs with immune checkpoint inhibitors and other targeted agents; conducting in-depth dissection of resistance mechanisms and designing next-generation ADC molecules capable of overcoming resistance; and optimizing dosing sequences and combination regimens to maximally delay resistance and enhance long-term survival benefits. As a sharp instrument in the era of precision medicine, the expansion of ADCs from HER2 to TROP2 not only validates the power of the translational medicine chain of “target discovery—drug design—clinical validation,” but also brings tangible hope to an ever-broader population of patients with solid tumors.

3. The Evolutionary Path of HER2-Targeted ADCs: From Companion Diagnostics, Drug Iterations, and Overcoming Drug Resistance to Pan-Tumor Expansion

HER2-targeted antibody–drug conjugates (ADCs), exemplified by T-DM1 (ado-trastuzumab emtansine, Kadcyla®) and T-DXd (trastuzumab deruxtecan, Enhertu®), have significantly reshaped the treatment landscape of breast cancer, offering entirely new therapeutic options for patients with both HER2-positive and HER2-low disease. However, with their increasingly widespread clinical use, several core challenges have emerged that urgently need to be addressed: how to precisely identify patient populations most likely to benefit, how to continuously advance drug optimization, how to effectively overcome drug resistance, and how to extend the success achieved in breast cancer to other tumor types. Centering on these four directions, four recent studies provide valuable cutting-edge evidence from the perspectives of diagnostics, drug development, fundamental mechanisms, and clinical translation.

Precise identification of patients who will benefit relies on the continuous optimization of companion diagnostic strategies. Egebjerg et al. investigated the companion diagnostic issues pertaining to HER2-targeted ADCs. The antitumor activity of ADCs is comprehensively influenced by multiple variables, including antibody affinity, linker stability, payload characteristics, drug-to-antibody ratio (DAR), and target expression level. Through an in-depth analysis of pivotal clinical trials of T-DM1 and T-DXd, the authors identified high HER2 expression (immunohistochemistry IHC 3+) as the core determinant of the efficacy of both agents across a range of solid tumor types, and the available evidence unequivocally supports the use of IHC as the primary companion diagnostic tool for patient selection. This conclusion is mechanistically plausible — the higher the antigen density on the target cell surface, the more efficient the antibody binding and subsequent internalization process, thereby amplifying the intracellular release of the payload and its ensuing cytotoxic effect. The review also systematically delineates the clinical utility of FDA-approved HER2 CDx assays, providing an operational guide for precisely pinpointing patient populations most likely to benefit from ADCs in clinical practice [3].

The development of next-generation ADCs continues to push the boundaries of therapeutic efficacy. The

review by Zimmerman and Esteva focuses on the latest advances in next-generation HER2-targeted ADCs in the field of breast cancer. Under the traditional treatment paradigm, patients with HER2-positive breast cancer rely on chemotherapy combined with anti-HER2 monoclonal antibodies; however, the intrinsic cytotoxicity of monoclonal antibodies alone is limited. T-DM1 and T-DXd integrate the targeting specificity of monoclonal antibodies with the potent killing capacity of small-molecule toxins through a linker, thereby achieving a synergistic effect of "precision guidance" and "high-efficiency destruction." This review comprehensively inventories next-generation HER2-targeted ADC candidates at the forefront of clinical development. These molecules feature systematic upgrades in antibody engineering, linker design, payload potency, and drug-to-antibody ratio (DAR) control, striving to enhance antitumor activity while reducing systemic toxicity. Furthermore, to address acquired resistance to T-DM1 and T-DXd, multiple combination therapies and sequential strategies are undergoing accelerated clinical validation. These studies are of critical importance for elucidating the evolutionary trajectories of resistance, optimizing treatment regimens, and identifying the patient subpopulations most likely to benefit [4].

In-depth elucidation of resistance mechanisms has opened new avenues for overcoming therapeutic bottlenecks. A research team systematically investigated the feasibility of targeting DNA repair pathways as a sensitization strategy in HER2-overexpressing breast cancer models with dual resistance to both T-DM1 and T-DXd. The results revealed that DNA damage repair mechanisms, particularly homologous recombination repair, are aberrantly activated in drug-resistant cells, constituting a core survival strategy that enables tumors to escape the DNA damage induced by the ADC payload, a topoisomerase I inhibitor. Based on this mechanistic insight, combining a DNA repair pathway inhibitor, such as a PARP inhibitor, significantly restored the sensitivity of resistant cells to T-DXd and produced a synergistic antitumor effect. This finding moves beyond the conventional approach of solely modifying the ADC molecule to counter resistance, and instead proposes a novel strategy of “jointly targeting tumor DNA repair vulnerabilities,” providing a feasible direction for subsequent therapy after T-DXd treatment failure [5].Therapeutic monoclonal antibodies exert their antitumor activity through four core pathways: direct target-mediated killing, immune-mediated killing, vascular and stromal modulation, and delivery of cytotoxic payloads. At the direct-acting level, monoclonal antibodies can block growth factor signaling, ligand-independent receptor activation, or directly induce apoptosis. Trastuzumab, for example, exerts its effects by blocking HER2 homodimerization and inhibiting downstream PI3K/AKT and MAPK pathways. Immune-mediated mechanisms include antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and antibody-dependent cellular phagocytosis (ADCP), among which NK cell-mediated ADCC is considered a central component of trastuzumab’s efficacy. Furthermore, anti-VEGF monoclonal antibodies can improve drug delivery by promoting vascular normalization [6].

Pan-cancer clinical evidence has fully substantiated the universal potential of the ADC therapeutic paradigm. Li et al. reported the DESTINY-Lung01 trial, the first large-scale prospective study to demonstrate significant efficacy of HER2-targeted therapy in non-small cell lung cancer (NSCLC). This international, multicenter, phase II trial enrolled 91 patients with metastatic HER2-mutant NSCLC who had progressed after prior standard therapy and received T-DXd monotherapy at 6.4 mg/kg. With regard to efficacy, the independently assessed objective response rate reached 55% (95% CI, 44–65), with a median duration of response of 9.3 months, median progression-free survival of 8.2 months, and median overall survival of 17.8 months. In terms of safety, the incidence of grade ≥3 drug-related adverse events was 46%, with neutropenia being the most common (19%); notably, the rate of drug-related interstitial lung disease (ILD) was 26%, including two fatal cases, underscoring the imperative to establish a rigorous pulmonary toxicity monitoring system when applying ADCs across tumor types. Biomarker analysis demonstrated that clear responses were observed irrespective of the HER2 mutation subtype, even in patients without detectable HER2 protein expression or gene amplification — a landmark finding that breaks away from the conventional framework that HER2-targeted therapy is applicable only to tumors with protein overexpression, extending the therapeutic targeting from "protein-level overexpression" to "gene-level mutation" and heralding a new era of ADC therapy for HER2-mutant solid tumors [7,8].

Antibody–drug conjugates (ADCs) possess the capacity to induce host antitumor immunity. In HER2-positive breast cancer models, T-DM1 not only kills cancer cells directly but also triggers canonical immunogenic cell death (ICD), characterized by calreticulin exposure and the release of HMGB1 and ATP. Critically, the ADC selectively eliminates the highly tumorigenic cancer stem cell (CSC) population, leading to a reduced proportion of $ALDH^+$ cells and impaired sphere-forming capacity. The immunological basis for this effect lies in the fact that antigens released from the killed CSCs are taken up and cross-presented by dendritic cells, thereby effectively activating $CD8^+$ T cell-mediated specific immune responses. In immunocompetent mice, the efficacy of T-DM1 is highly dependent on $CD8^+$ T cells and NK

cells, and long-term tumor control is markedly attenuated under immunodeficient conditions. This study profoundly reshapes the conceptual framework surrounding ADCs: they are not merely precision carriers of cytotoxic drugs, but also inducers of in situ tumor vaccines. The eradication of CSCs eliminates the “seeds” of recurrence, while the activation of adaptive immunity provides durable immune surveillance; together, these effects lay a solid theoretical foundation for the combination of ADCs with immune checkpoint inhibitors [9].

In terms of pan-cancer expansion, the multidimensional determinants of sensitivity to HER2-targeted ADCs in urothelial carcinoma provide mechanistic guidance for the precision application of these agents in this cancer type. Using patient-derived models and genomic analyses, the study confirmed that while HER2 gene amplification and protein expression level are fundamental predictive factors, they are not sufficient conditions; the expression levels of endocytosis-related genes directly influence the efficiency of ADC internalization, while lysosomal acidification capacity and proteolytic enzyme activity determine the adequacy of linker cleavage and payload release. Furthermore, homologous recombination deficiency status is associated with sensitivity to ADCs carrying topoisomerase I inhibitor payloads. Notably, some tumors with low HER2 expression can retain sensitivity to ADCs through an enhanced endocytosis–lysosomal pathway, providing a theoretical basis for expanding the population of patients who may benefit from ADCs in urothelial carcinoma. Concurrently, FGFR3 mutations were identified as potential co-existing drivers of ADC resistance, offering clues for combination targeting strategies [10].

4. Diversified Exploration of HER2-Targeted Therapy

Innovation in local drug delivery has opened a new dimension for the clinical application of ADCs. Researchers have focused on non-muscle-invasive bladder cancer (NMIBC), which has an exceedingly high recurrence rate—even after transurethral resection combined with Bacillus Calmette-Guérin (BCG) instillation, the 5-year recurrence rate remains as high as 55%–85%. The study systematically evaluated the antitumor activity and safety of intravesical instillation of the HER2-targeted ADC RC48-ADC (disitamab vedotin). In NMIBC, the proportions of HER2 1+, 2+, and 3+ were 16.7%, 56.2%, and 14.6%, respectively. The antitumor effect of RC48-ADC was positively correlated with the level of HER2 expression and was exerted through the induction of G2/M phase arrest and caspase-dependent apoptosis. In an orthotopic bladder cancer model, intravesical instillation of RC48-ADC significantly inhibited tumor growth, and its efficacy was superior to that of disitamab alone, MMAE alone, epirubicin, and phosphate-buffered saline, with a favorable safety profile within the effective dose range. This study provides solid preclinical evidence for the clinical translation of intravesical RC48-ADC therapy for NMIBC, demonstrating the potential of ADCs to extend from systemic administration to regional precision therapy [11].

Sustained therapeutic efficacy cannot be achieved without systematic management of safety. At present, T-DXd and T-DM1 have been approved, and more than 60 ADC candidates are under development. For T-DM1, whether administered as monotherapy or in combination, in adjuvant, neoadjuvant, or first-/second-line settings, commonly reported adverse events include epistaxis, fatigue, headache, nausea, and pyrexia. The toxicity profile of T-DXd is predominantly characterized by alopecia, cytopenias, decreased appetite, fatigue, and gastrointestinal reactions. The review emphasizes that although HER2-targeted ADCs have demonstrated clear clinical benefit in breast cancer, multiple systemic and organ-specific adverse events, including dose-limiting toxicities, have been frequently reported even at suboptimal doses, posing a considerable obstacle to maximizing efficacy through dose escalation. Therefore, "precision medication" entails not only the identification of patients likely to benefit, but also individualized toxicity risk management, providing an important reference for clinical toxicity monitoring and control [12,13].

With regard to the cardiotoxicity of HER2-targeted ADCs, pooled results from multiple trials indicate an all-grade cardiac adverse event incidence of 5.83%, with grade ≥3 events occurring at 0.68%; T-DXd exhibits a slightly higher cardiotoxicity signal compared with T-DM1, with decreased left ventricular ejection fraction being the most common manifestation. Notably, the majority of cardiac events occur within months to one year after treatment, suggesting the necessity of long-term cardiac function monitoring rather than a sole focus on the acute phase; a prior history of anthracycline or trastuzumab exposure further elevates the risk. This provides a critical reference for clinical practice—although the overall cardiotoxicity of HER2-targeted ADCs is lower than that of conventional regimens, as the duration of treatment with highly potent ADCs such as T-DXd extends, cardiovascular safety must be integrated into comprehensive disease management, particularly for breast cancer patients with underlying cardiovascular disease or a history of prior cardiotoxic exposure. Concurrently, Fu et al. (2023) directly confronted the most severe safety endpoint by quantifying the risk of fatal adverse events through a systematic review and meta-analysis of randomized controlled trials. The overall incidence of fatal events with HER2-targeted ADC therapy

was 3.2%, with a relative risk of 1.68 compared with the control group. Interstitial lung disease/pneumonitis ranked as the leading cause of death, followed by infection, cardiac disease, and hemorrhage. T-DXd was particularly notable for fatal interstitial pneumonitis, owing to its potent off-target toxicity and potential pulmonary toxicity. The disparities in the spectra of fatal events across different ADCs suggest that the nature of the payload, linker stability, and the bystander effect collectively shape the toxicity profile [14].

Innovation in molecular design is a key driving force for overcoming the bottleneck of drug resistance. A bivalent dual-targeting ADC can simultaneously bind two non-overlapping epitopes on the HER2 receptor. This unique binding mode induces receptor clustering, thereby enhancing endocytosis, lysosomal trafficking, and degradation. When conjugated to a microtubule inhibitor, this biparatopic ADC demonstrated superior antitumor activity compared with T-DM1 in tumor models derived from multiple patient subgroups, covering populations suitable for T-DM1, unsuitable for T-DM1, and those with resistance or relapse. Study B indicates that promoting receptor clustering to enhance endocytic efficiency can achieve more efficient payload delivery and broader tumor cell killing, offering a new option for overcoming T-DM1 resistance [15].

The discovery of HER2 and the advent of targeted therapy have reshaped the treatment landscape of HER2-positive breast cancer; however, HER2-low and heterogeneous expression are attracting increasing attention. HER2 heterogeneity can be detected by conventional IHC, gene expression profiling, and other techniques, and extensive evidence has demonstrated its association with shorter disease-free survival and overall survival. With the emergence of more potent next-generation ADCs, targeting HER2 in tumors traditionally classified as "HER2-negative" but harboring "HER2-low" expression has become feasible. The review calls for an optimized nomenclature system for HER2 expression, enabling clinicians to formulate optimal strategies based on expression profiles. Concurrently, the techniques for detecting HER2 heterogeneity still require validation, and novel agents capable of effectively addressing tumors with heterogeneous expression must be developed in parallel. This challenge precisely underscores the unique value of ADCs with a bystander effect, such as T-DXd, in the HER2-low population [16,17].

Small-molecule targeted agents offer a convenient oral alternative for patients with HER2-mutant lung cancer. A study has demonstrated the efficacy of the oral reversible tyrosine kinase inhibitor sevabertinib in advanced HER2-mutant non-small cell lung cancer (NSCLC), a mutation found in 2%–4% of patients. This open-label, multicenter, multi-cohort phase I–II study comprised three cohorts: Cohort D enrolled patients with no prior HER2-targeted therapy, Cohort E enrolled those previously treated with a HER2-targeted ADC, and Cohort F enrolled treatment-naïve patients. As of June 27, 2025, a total of 209 patients had received sevabertinib 20 mg twice daily. At a median follow-up of 13.8 months, the objective response rate (ORR) in Cohort D (n=81) was 64% (95% CI, 53–75), with a median duration of response of 9.2 months and a median progression-free survival of 8.3 months; the ORR in Cohort E (n=55) was 38% (95% CI, 25–52). Sevabertinib retained activity in patients previously treated with ADCs, and its oral route of administration provides a more convenient treatment option, establishing a complementary therapeutic sequence with ADCs [18].

5. Future Perspectives

In the future, HER2-targeted ADCs will continue to advance along four major directions: greater precision, enhanced efficacy, reduced toxicity, and broadened spectrum. Companion diagnostics will evolve from sole reliance on protein expression or gene amplification testing toward the integration of multidimensional functional biomarkers—such as endocytic pathway activity, lysosomal function, and DNA repair deficiency—to enable more precise identification of patient populations likely to benefit. Next-generation molecular designs, represented by bispecific/biparatopic ADCs, conjugates armed with novel payloads (e.g., immune agonists or RNA polymerase inhibitors), and site-specific conjugation technologies, strive to enhance antitumor activity while simultaneously reducing systemic off-target toxicity. Building upon this foundation, combination strategies targeting resistance mechanisms will increasingly take center stage: the combination of ADCs with immune checkpoint inhibitors is intended to convert ADC-induced immunogenic cell death into durable adaptive antitumor immunity; synergy with DNA damage repair inhibitors can overcome acquired resistance to topoisomerase I inhibitor-based payloads; and sequential or combined use with small-molecule targeted agents such as tyrosine kinase inhibitors holds promise for weaving together a management paradigm that spans the entire disease course. Meanwhile, drawing on the development experience of TROP2-targeted ADCs, identifying ideal targets shared across tumor types and establishing dynamically monitorable efficacy predictors will propel ADCs from “single-tumor precision therapy” toward “pan-tumor broad-coverage therapy.” With regard to safety management, it is imperative to expeditiously construct a comprehensive toxicity surveillance system and standardized early intervention protocols encompassing vital organs such as the lungs and heart, and to integrate measures such as local drug delivery and optimized dosing sched-

ules to maximally widen the therapeutic window. In summary, ADCs are evolving from mere "biological missiles" that simply deliver cytotoxic drugs into integrated therapeutic platforms endowed with immunomodulatory capabilities, the capacity to remodel the tumor microenvironment, and the functionality for sequential synergistic effects, thereby holding the promise of delivering durable survival benefits to patients with HER2-altered tumors and a broader spectrum of solid tumors.

6. Conclusion

Antibody–drug conjugates (ADCs) have fundamentally reshaped the treatment paradigm for HER2-altered solid tumors by integrating the target-recognition capability of monoclonal antibodies with the potent cytotoxicity of small-molecule chemotherapeutic agents. The first-generation ADC, T-DM1, was the first to validate the feasibility of this drug class in solid tumors, while the next-generation agent T-DXd, leveraging an enzyme-cleavable linker, a higher drug-to-antibody ratio (DAR), and a distinctive bystander killing effect, has extended the beneficiary population from those with HER2-high expression to those with HER2-low expression. T-DXd has also achieved breakthroughs in tumor types such as HER2-mutant non-small cell lung cancer, realizing a leap from targeting protein overexpression to targeting driver gene alterations. In terms of companion diagnostics, immunohistochemistry-based assessment of HER2 overexpression remains the core approach for identifying the predominant beneficiary population; however, HER2 mutation has been validated as an independent therapeutic target, underscoring the necessity of establishing a more refined stratification system. With respect to drug resistance, loss of the target antigen, upregulation of drug efflux pumps, and compensatory activation of DNA damage repair pathways represent key drivers of multidrug resistance, and strategies that combine PARP inhibitors to block DNA repair have already demonstrated sensitizing potential. The toxicity profile has also become increasingly clear: interstitial lung disease, cardiotoxicity, and cytopenias constitute the principal dose-limiting events, among which fatal interstitial pneumonitis requires particularly stringent surveillance when T-DXd is administered. Furthermore, biparatopic ADCs enhance endocytosis and tumor cell killing by inducing receptor aggregation; local intravesical instillation provides a novel interventional modality for high-risk non-muscle-invasive bladder cancer; and the oral tyrosine kinase inhibitor sevabertinib retains antitumor activity in ADC-pretreated HER2-mutant lung cancer, establishing a sequential or complementary therapeutic ladder between ADCs and small-molecule drugs. The rise of TROP2-targeted ADCs further broadens the prospect of "pan-tumor" applications.

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