Breast Cancer: Targets and Therapy

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REVIEW

Comparative Analysis and Future Prospects of Human Epidermal Growth Factor Receptor 2 (HER2) and Trophoblast Cell-Surface Antigen 2 (Trop-2) Targeted Antibody-Drug Conjugates in Breast Cancer Treatment

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Abstract: Breast cancer remains the most prevalent malignancy among women globally, presenting significant challenges in therapeutic strategies due to tumor heterogeneity, drug resistance, and adverse side effects. Recent advances in targeted therapies, particularly antibody-drug conjugates (ADCs), have shown promise in addressing these challenges by selectively targeting tumor cells while sparing normal tissues. This study provides a comprehensive analysis of two innovative ADCs targeting HER2 and Trop-2, which are critical markers in various breast cancer subtypes. These conjugates combine potent cytotoxic drugs with specific antibodies, leveraging the antigens' differential expression to enhance therapeutic efficacy and reduce systemic toxicity. Our comparative analysis highlights the clinical applications, efficacy, and safety profiles of these ADCs, drawing on data from recent clinical trials. In addition, the paper discusses the potential of these ADCs in treating other types of cancers where HER2 and Trop-2 are expressed, as well as the toxicity risks associated with targeting these antigens in normal cells. Additionally, the paper discusses novel synthetic drugs that show potential in preclinical models, focusing on their mechanisms of action and therapeutic advantages over traditional chemotherapy. The findings underscore the transformative impact of targeted ADCs in breast cancer treatment, noting significant advancements in patient outcomes and management of side effects. However, ongoing issues such as resistance mechanisms and long-term safety remain challenges. The conclusion offers a forward-looking perspective on potential improvements and the future trajectory of ADC research. This study not only elucidates the current landscape of ADCs in breast cancer but also sets the stage for the next generation of oncological therapeutics. This study not only elucidates the current landscape of ADCs in breast cancer but also sets the stage for the next generation of oncological therapeutics, with particular attention to their broader applications and associated risks.

Keywords: breast cancer, antibody drugs, HER2, Trop-2

Introduction

Breast cancer is the most prevalent malignancy among women globally, representing a significant public health challenge with high morbidity and mortality rates.[1] The heterogeneity of breast cancer, characterized by diverse molecular subtypes, complicates therapeutic strategies and necessitates personalized treatment approaches.[2] Among these subtypes, the overexpression of human epidermal growth factor receptor 2 (HER2) and trophoblast cell-surface antigen 2 (Trop-2) are particularly notable due to their associations with aggressive cancer phenotypes and poor prognoses.[3,4]

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Recent advancements in oncology have led to the development of targeted therapies, particularly antibody-drug conjugates (ADCs). These therapies combine the specificity of monoclonal antibodies with the potent cytotoxic effects of chemotherapeutic agents, thereby maximizing tumor eradication while minimizing systemic toxicity.[5] HER2-targeted therapies have revolutionized the treatment of HER2-positive breast cancer, with agents like trastuzumab serving as the foundation for more advanced ADCs such as trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd). T-DM1, which combines trastuzumab with the microtubule inhibitor DM1 via a stable linker, has shown superior efficacy and safety in treating HER2-positive advanced breast cancer.[6,7] Similarly, T-DXd, which links trastuzumab to the topoisomerase I inhibitor DXd, has demonstrated significant improvements in progression-free survival and overall survival in patients who have previously been treated with other HER2-targeted therapies.[7–9] Beyond breast cancer, HER2 is also overexpressed in other malignancies such as gastric and ovarian cancers, making these ADCs potential candidates for broader oncological applications. However, the expression of HER2 in normal tissues raises concerns about off-target toxicity, necessitating careful evaluation of these therapies in clinical settings.

Trop-2 is another promising target for ADC therapy due to its high expression in several epithelial cancers, including triple-negative breast cancer (TNBC), which lacks effective targeted therapies due to the absence of estrogen, progesterone, and HER2 receptors.[10,11] Sacituzumab govitecan, an ADC targeting Trop-2, has shown significant promise in clinical trials by delivering the cytotoxic agent SN-38 directly to cancer cells, resulting in improved progression-free and overall survival in patients with metastatic TNBC.[12–15] Beyond TNBC, Trop-2 is also overexpressed in other epithelial cancers such as urothelial and non-small cell lung cancers, making it a potential target for ADCs in these malignancies. However, Trop-2 expression in normal tissues poses a risk for off-target toxicity, which warrants further investigation in clinical settings.

This study aims to provide a comprehensive analysis of the clinical applications, efficacy, and safety profiles of ADCs targeting HER2 and Trop-2 in breast cancer treatment. Additionally, it explores the potential applications of these ADCs in other cancers, particularly focusing on the associated toxicity when targeting normal cells expressing HER2 and Trop-2. By reviewing recent clinical trials and preclinical models, we seek to elucidate the mechanisms of action, therapeutic advantages, and ongoing challenges associated with these novel therapies. This analysis underscores the transformative impact of ADCs in breast cancer treatment and offers insights into future therapeutic developments,[16] as well as the broader implications of ADC research across different cancer types.

Artificial Synthesis of New Drugs with New Modes of Action

While not directly related to ADCs, these novel synthetic agents offer complementary approaches that could be integrated with ADC-based strategies to enhance therapeutic outcomes. For instance, ERα degraders might be used alongside ADCs targeting HER2 in hormone receptor-positive breast cancers, potentially overcoming resistance mechanisms and improving efficacy. Similarly, hypoxia-selective antitumor agents could be combined with ADCs to target hypoxic tumor microenvironments, which are often resistant to standard therapies.

Novel ERα-Degrading Agents

Estrogen receptor alpha (ERα) plays a pivotal role in the proliferation and progression of hormone receptor-positive breast cancer, which accounts for approximately 70% of all breast cancer cases.[1] Conventional therapies targeting ERα, primarily involving antagonists and inhibitors, face limitations due to resistance mechanisms that decrease their efficacy over time.[17] To overcome these challenges, novel ERα degraders have been synthesized to induce the degradation of ERα protein itself, rather than merely inhibiting its activity. These advancements are particularly relevant when considering combination strategies with ADCs targeting HER2, as such integrative approaches may enhance therapeutic efficacy, especially in hormone receptor-positive/HER2-positive breast cancer subtypes.[18]

One such promising agent is sodium 320(R)-dihydroxy-19-estradiol (Kuz7), a derivative of the natural hormone estradiol. This compound enhances nucleophilicity and lipophilicity by introducing a second hydroxyl group and a thickened ring at the 17th position side chain. In vitro studies have shown that Kuz7 exhibits potent cytotoxicity against HR-positive breast cancer cells, such as MCF-7, while demonstrating minimal toxicity towards normal mammary epithelial cells (MCF-10A). By inducing the degradation of ERα, Kuz7 disrupts the cell cycle and promotes apoptosis, making it a significant advancement over existing ERα-targeting therapies.[19,20] Moreover, the integration of Kuz7 with

ADCs targeting HER2 in HR-positive/HER2-positive breast cancer could potentially enhance therapeutic outcomes by simultaneously targeting multiple pathways involved in tumor progression.

Moreover, the development of proteolysis-targeting chimeras (PROTACs) has introduced a novel approach to ERα degradation. PROTACs are bifunctional molecules that recruit an E3 ligase to the target protein, leading to its ubiquitination and subsequent degradation by the proteasome. While PROTACs represent a promising strategy in combating endocrine resistance, their relevance to this review lies in potential synergies with ADCs targeting HER2. Combining these approaches could enhance treatment efficacy in hormone receptor-positive/HER2-positive breast cancer by simultaneously targeting multiple oncogenic pathways.

Recent studies have highlighted the potential of orally bioavailable selective estrogen receptor degraders (SERDs) such as elacestrant (RAD-1901), which have demonstrated efficacy in both in vitro and in vivo models of ER-positive breast cancer. These advancements offer new hope for patients with endocrine-resistant breast cancer, providing more effective and convenient treatment options.[20,21] While SERDs like elacestrant show promise in addressing endocrine resistance, their integration with ADCs targeting HER2 could further enhance therapeutic outcomes, especially in hormone receptor-positive /HER2-positive breast cancer subtypes, by leveraging complementary mechanisms of action.

Novel Hypoxia-Selective Antitumor Agents

Hypoxia within the tumor microenvironment drives cancer progression by promoting angiogenesis, metastasis, and resistance to therapy.[22] Addressing this, researchers have developed hypoxia-selective antitumor drugs that are activated in the low-oxygen conditions typical of solid tumors. These agents aim to selectively kill hypoxic tumor cells without affecting the oxygenated normal tissues.[17] The potential for combining hypoxia-selective antitumor drugs with ADCs targeting HER2 could provide a dual-targeting strategy, enhancing the efficacy of treatment by addressing both the hypoxic microenvironment and HER2-positive tumor cells simultaneously.

The synthesized class of 6-aminoquinoxaline-2-cyanonitrile 1,4-dioxane derivatives exemplifies this approach. These compounds are designed to release cytotoxic agents under hypoxic conditions, thus targeting the hypoxic zones within tumors effectively. Preclinical evaluations indicate that these drugs significantly inhibit the proliferation of both HR-positive and HR-negative breast cancer cells under hypoxic conditions, showcasing their potential as effective treatments for aggressive and resistant forms of breast cancer.[19] Moreover, combining these hypoxia-activated drugs with HER2-targeted ADCs could enhance therapeutic efficacy by simultaneously addressing tumor hypoxia and HER2 overexpression, offering a promising strategy for treating resistant breast cancer subtypes.[23]

One promising HAP is tirapazamine, which has shown efficacy in targeting hypoxic cells and enhancing the effectiveness of radiation therapy and chemotherapy in breast cancer models.[24] Additionally, combining tirapazamine with HER2-targeted ADCs may provide a synergistic approach, improving treatment outcomes by addressing both hypoxia and HER2 overexpression in breast cancer tumors.[25]

Recent research has highlighted the role of hypoxia-inducible factors (HIFs), particularly HIF-1α, in regulating tumor responses to hypoxia. Inhibitors targeting HIF-1α, such as PX-478, have shown significant antitumor activity by reducing angiogenesis and enhancing the sensitivity of tumor cells to chemotherapy.[26–29] Moreover, the integration of HIF inhibitors with HER2-targeted ADCs could enhance treatment efficacy by simultaneously targeting the hypoxic microenvironment and HER2-positive tumor cells, offering a multifaceted approach to managing resistant breast cancer.[30]

HIFs are stabilized under hypoxic conditions, allowing them to regulate a variety of genes involved in crucial cancer processes such as angiogenesis, cell survival, and metabolism. The activation of HIF-1α leads to the transcription of genes that promote tumor growth and adaptation to low oxygen environments.[26,27] Inhibitors like PX-478 disrupt these pathways, thereby reducing the tumor's ability to thrive in hypoxic conditions.[31] Combining PX-478 with HER2-targeted ADCs could offer a synergistic approach, enhancing the overall efficacy by simultaneously disrupting hypoxia-driven pathways and directly targeting HER2-positive cancer cells.[32]

Antibody-Drug Conjugates (ADCs) Targeting HER2

HER2 is a transmembrane tyrosine kinase receptor and a member of the human epidermal growth factor receptor (EGFR) family, with overexpression or amplification occurring in about 20% of breast cancers. This overexpression leads to

tumor cell proliferation, invasion, metastasis, and drug resistance, resulting in poor prognosis.[33] Antibody-drug conjugates (ADCs) targeting HER2 combine a monoclonal antibody with a cytotoxic drug via a chemical linker, which specifically recognizes and binds HER2-positive tumor cells. Upon internalization, the drug is released, achieving selective cytotoxicity while minimizing damage to normal tissues.[34] Furthermore, the combination of HER2-targeted ADCs with other therapeutic agents, such as immune checkpoint inhibitors or hypoxia-targeted therapies, is being explored to overcome resistance mechanisms and enhance overall efficacy in HER2-positive breast cancer.[7]

Two ADCs targeting HER2 have been clinically approved: trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd). T-DM1 combines trastuzumab with the microtubule inhibitor DM1, demonstrating superior efficacy and safety compared to standard therapies.[35] T-DXd links trastuzumab to the topoisomerase I inhibitor DXd, showing significant improvements in progression-free survival and overall survival in patients who have previously been treated with other HER2-targeted therapies.[36] Additionally, ongoing research is investigating the combination of these ADCs with other therapeutic agents, such as PARP inhibitors or immune checkpoint inhibitors, to further enhance their efficacy and overcome resistance mechanisms.[37]

Structure of ADCs

ADCs consist of three main components: a monoclonal antibody, a cytotoxic drug (payload), and a chemical linker. Trastuzumab or its variants are typically used for HER2-targeting ADCs due to their high affinity for HER2 and their ability to modulate HER2 signaling pathways.[38] The payloads include microtubule inhibitors, topoisomerase I inhibitors, and DNA cross-linkers, capable of killing tumor cells at low concentrations.[39] The linkers can be cleavable or non-cleavable, with cleavable linkers releasing the drug inside tumor cells and non-cleavable linkers releasing the drug-linker complex.

Advancements in linker and payload technologies have improved the stability, potency, and homogeneity of ADCs. Second and third-generation ADCs exhibit enhanced therapeutic efficacy and reduced toxicity.[40] Current research focuses on developing novel ADCs with optimized antibodies, linkers, and payloads to improve the treatment of HER2-positive breast cancer.[41]

Mechanism of Action of ADCs Targeting HER2

The mechanism of action of ADCs targeting HER2 primarily involves the following steps:1. Binding to HER2: The ADC binds to HER2 on the surface of tumor cells through its antibody component, achieving specific recognition and targeting.[42] 2. Internalization and Degradation: The ADC-HER2 complex is internalized by the tumor cell and trafficked to endosomes and lysosomes, where it is degraded.[43] 3. Release of the Payload: The cytotoxic payload is released within the tumor cell, where it exerts its effects. These effects include inhibiting microtubule polymerization, blocking DNA replication, and inducing DNA breaks.[44] 4.Bystander Effect: The released payload can diffuse through the cell membrane into neighboring tumor cells, including HER2 low-expressing or negative tumor cells, thereby exerting a killing effect on these cells as well. Recent studies are focusing on optimizing the bystander effect to enhance efficacy while minimizing off-target toxicity, aiming to improve the therapeutic index of ADCs targeting HER2.[6]

Further details on the bystander effect indicate its significant role in improving the therapeutic index of ADCs. The phenomenon allows ADCs to target not only the HER2-expressing cells but also adjacent cells that may not express HER2, thereby addressing intratumoral heterogeneity.[45]

Moreover, optimizing the bystander effect could help reduce off-target effects, thereby improving the safety profile of ADCs. Recent studies have also highlighted the structural dynamics involved in ADC mechanisms. Structural analyses reveal how HER2 heterodimers and homodimers function, providing insights into the conformational changes that facilitate ADC binding and internalization.[46] These structural insights are crucial for designing next-generation ADCs with improved binding efficiency and therapeutic outcomes.[43]

Moreover, advancements in ADC design, such as optimized linkers and novel cytotoxic agents, have further improved the stability and efficacy of these therapies. New generations of ADCs are designed to release their payload more efficiently within the tumor microenvironment, minimizing systemic toxicity.[47]

Clinical Trials of ADCs Targeting HER2

Two ADCs targeting HER2, T-DM1 and T-DXd, have been clinically approved and have demonstrated significant clinical efficacy and a manageable safety profile in metastatic or locally advanced HER2-positive breast cancer. Additionally, several novel ADCs targeting HER2 are under preclinical or clinical investigation, offering potential improvements in antibodies, linkers, or payloads, and are expected to provide more therapeutic options for breast cancer patients. These investigational ADCs aim to overcome limitations observed with current therapies, such as resistance mechanisms or off-target toxicities, by incorporating novel technologies and design strategies. This ongoing research holds promise for expanding the arsenal of effective treatments for HER2-positive breast cancer.

T-DM1

T-DM1 is an ADC that combines trastuzumab with the microtubule inhibitor DM1 via a thioether non-cleavable linker and is one of the first clinically approved ADCs targeting HER2. T-DM1 has shown superior efficacy and safety compared to trastuzumab combined with paclitaxel or capecitabine combined with lapatinib in metastatic or locally advanced HER2-positive breast cancer. It has become a standard second- or third-line treatment option for these patients. T-DM1 has also been clinically tested in early-stage HER2-positive breast cancers at high risk for residual disease, significantly reducing the risk of recurrence or death, and improving disease-free survival and overall survival.[48] Additionally, combining T-DM1 with tucatinib, a HER2-selective tyrosine kinase inhibitor, has shown increased antitumor activity in preclinical models, suggesting potential benefits of combination therapies. However, despite its success, resistance to T-DM1 can develop, and ongoing research is focused on understanding these mechanisms and exploring combination therapies to overcome resistance. Early studies combining T-DM1 with tucatinib, a HER2-selective tyrosine kinase inhibitor, have shown promise in enhancing antitumor activity, indicating potential clinical benefits of such strategies.[49]

T-DXd

T-DXd is an ADC that combines trastuzumab with the topoisomerase I inhibitor DXd via a tetrapeptidyl cleavable linker. It is one of the newest clinically approved ADCs targeting HER2, featuring a higher drug-to-antibody ratio, stronger membrane-permeable payload, and better stability, resulting in higher and broader activity. T-DXd has demonstrated superior efficacy and safety compared to trastuzumab in combination with capecitabine or venetoclax in metastatic or locally advanced HER2-positive breast cancer, and has become a standard of care for second- or third-line treatment of these patients. T-DXd has also been clinically tested in early-stage HER2-positive breast cancers at high risk for residual disease, showing that it significantly reduces the risk of recurrence or death, and improves disease-free survival and overall survival.[50,51] Ongoing research is focused on optimizing the use of T-DXd, including its combination with other therapeutic agents, to further enhance its efficacy and overcome potential resistance mechanisms.[7]

The DESTINY-Breast01 trial was a multicenter, single-arm, two-stage Phase II trial designed to evaluate the efficacy and safety of T-DXd in patients with metastatic or locally advanced HER2-positive breast cancer who had failed at least two standard chemotherapy regimens. The trial enrolled 253 HER2-positive (IHC 3+ or FISH+) patients, of whom 184 were HR-negative and 69 were HR-positive. Patients were treated with T-DXd (5.4 mg/kg every 3 weeks) until disease progression or unacceptable toxicity. The primary endpoint was the overall response rate (ORR), and secondary endpoints included progression-free survival (PFS), overall survival (OS), disease control rate (DCR), complete response rate (CRR), duration of response, safety, and quality of life. The final results of the trial showed an ORR of 61.4% in the T-DXd group, with a complete remission rate of 6.3% and a partial remission rate of 55.1%. The median PFS was 19.4 months, while the median OS had not been reached at the time of analysis. The PFS and OS in the T-DXd group were 19.4 months and did not reach the median, respectively. The DCR and CRR were 97.6% and 54.5%, respectively. Adverse events mainly included nausea (79.8%), anemia (64.4%), vomiting (48.6%), and neutropenia (45.8%). Despite the promising results, interstitial lung disease (ILD) was observed in some patients, which is a serious adverse event requiring close monitoring.[52,53]

These results suggest that T-DXd is an effective and safe treatment for metastatic or locally advanced HER2-positive breast cancer, providing a new treatment option for these patients. However, careful monitoring for serious adverse events, such as interstitial lung disease (ILD), is essential. T-DXd is also currently in clinical trials for other tumor types and early-stage breast cancer.

Antibody-Drug Conjugates Targeting Trop-2

Trop-2, a cell surface glycoprotein, is overexpressed in several epithelial cancers, including triple-negative breast cancer (TNBC), where it is associated with poor prognosis and aggressive disease.[54] This overexpression makes Trop-2 an attractive target for ADC therapies, designed to deliver cytotoxic agents directly to tumor cells. By specifically targeting Trop-2, ADCs can potentially overcome the challenges posed by the lack of targeted therapies in TNBC, offering a promising treatment strategy for this aggressive breast cancer subtype.

Mechanism of Action and Development

Sacituzumab Govitecan (SG), a leading ADC targeting Trop-2, exemplifies the innovative approach to cancer treatment using ADCs. SG consists of an anti-Trop-2 antibody conjugated to the topoisomerase inhibitor SN-38, the active metabolite of irinotecan, through a hydrolyzable linker. This configuration allows SN-38 to be released selectively within the tumor environment upon internalization and binding of the ADC, ensuring a high local concentration of the cytotoxic agent[55]. By selectively targeting Trop-2, SG enhances antitumor activity while aiming to reduce the adverse effects typically associated with systemic chemotherapy, making it a promising treatment option for aggressive cancers such as triple-negative breast cancer (TNBC).

Clinical Efficacy and Trials

The efficacy of Sacituzumab Govitecan (SG) has been extensively evaluated in clinical trials, most notably in the ASCENT trial, which focused on patients with metastatic triple-negative breast cancer (TNBC) who had received multiple prior treatments. This pivotal Phase III study demonstrated significant clinical benefits of SG over standard chemotherapy regimens, highlighting its potential as a transformative treatment for this aggressive breast cancer subtype. The ASCENT trial was a multicenter, randomized, open-label phase III study designed to assess the efficacy and safety of SG in patients with metastatic TNBC. The trial enrolled 529 patients who had received at least two prior therapies for metastatic disease. Patients were randomized to receive either SG or the physician's choice of single-agent chemotherapy. The primary endpoint was progression-free survival (PFS), with secondary endpoints including overall survival (OS), objective response rate (ORR), and safety. SG significantly improved PFS compared to standard chemotherapy. The median PFS for the SG group was 5.6 months, versus 1.7 months for the chemotherapy group ($P < 0.001$).[34,56] SG also demonstrated a substantial improvement in OS. The median OS for patients treated with SG was 12.1 months, compared to 6.7 months for those receiving chemotherapy ($P < 0.001$).[57] The ORR was significantly higher in the SG group, with a response rate of 35% compared to 5% in the chemotherapy group, indicating more substantial tumor reduction with SG treatment. SG exhibited a manageable safety profile with common adverse events including neutropenia, diarrhea, and nausea, which were generally predictable and controllable.[58] Despite these promising results, resistance to SG remains a concern, and ongoing studies are exploring combination strategies to enhance its efficacy. Recent studies have explored combining SG with other therapeutic agents to enhance its efficacy and overcome resistance. For example, a Phase I trial investigated the combination of SG with berzosertib, an ATR (Ataxia Telangiectasia and Rad3-related) inhibitor, to target replication stress and chemotherapy resistance. This combination was well tolerated and showed promising antitumor activity, suggesting potential for further development in treating aggressive cancers.[59]

Future Perspectives and Challenges

Despite the promising results, the journey of optimizing Trop-2 targeted ADCs like Sacituzumab Govitecan (SG) is ongoing. Challenges such as developing resistance, optimizing drug-linker stability, and managing off-target effects continue to drive research. Specifically, resistance to ADCs can arise from various mechanisms, including alterations in antigen expression, increased drug efflux, and changes in intracellular drug processing. These challenges highlight the need for continued innovation in ADC design and combination strategies to sustain their efficacy.[60]

Future strategies to overcome these challenges include modifying the linker chemistry to improve stability and payload delivery.Enhancements in linker design are particularly crucial, as they can lead to better control over the release of cytotoxic agents, ensuring that the drug remains stable in circulation and is efficiently released within the tumor microenvironment.[61]

Additionally, combining ADCs with other therapeutic modalities, such as immune checkpoint inhibitors, is being explored to enhance efficacy and overcome resistance mechanisms. The rationale behind this approach is to simultaneously target different aspects of tumor biology, potentially leading to more durable and comprehensive treatment outcomes.[62]

Further, expanding the application of Trop-2 targeting ADCs to other Trop-2 expressing tumors and investigating their use in earlier lines of therapy are areas of active investigation. Extending the use of Trop-2 ADCs beyond breast cancer to other cancers with high Trop-2 expression, such as lung and gastric cancers, could significantly broaden the impact of this therapeutic strategy in oncology.[63] Preclinical studies and early-phase clinical trials are evaluating the effectiveness of Trop-2 ADCs in other solid tumors, which could lead to new indications for these treatments.[64]

Conclusion and Future Prospects

The development and application of antibody-drug conjugates (ADCs) targeting HER2 and Trop-2 represent significant advancements in the treatment of breast cancer, particularly for subtypes such as HER2-positive and triple-negative breast cancer (TNBC) that are associated with poor prognosis and limited therapeutic options. As summarized in Table 1, ADCs like trastuzumab emtansine (T-DM1), trastuzumab deruxtecan (T-DXd), and sacituzumab govitecan (SG) have not only demonstrated remarkable clinical efficacy but also exhibited manageable safety profiles, revolutionizing the therapeutic landscape for these challenging cancer subtypes.

Table 1 Summary of Novel Drugs with Artificially Synthesized New Modes of Action and Antibody-Drug Conjugates

Drug Name	Mechanism of Action	Target	Clinical Trial Stage	Efficacy and Safety
Sodium 3,20(R)-dihydroxy -19-estradiol	ERα degraders that induce ubiquitination and proteasomal degradation of ERα, thereby inhibiting the ERα signaling pathway	ERα	Period I	Demonstrated good tolerability and anti-tumor activity in HR-positive/HER2-negative patients with advanced breast cancer
6(7)-Aminoquinoxaline -2-carbonitrile 1,4-dioxane derivative	Hypoxia-selective antitumor drugs that are able to release DNA cross-linking agents under hypoxic conditions, leading to tumor cell death	DNA	Period II	Combination therapy with docetaxel in patients with TNBC showed higher objective remission rates and progression-free survival, but also increased moderate or severe hematologic and non-hematologic toxicity
Trastuzumab emtansine (T-DM1)	ADC, consisting of Trastuzumab, a HER2-specific antibody, and Emtansine, a microtubule stabilizer, inhibits tumor cell division and proliferation by delivering Emtansine to tumor cells through HER2-mediated endocytosis.	HER2	Marketed	Significantly Improved Overall Survival and Progression-Free Survival with Lower Toxicity Compared to Trastuzumab or Lapatinib Alone in HER2-Positive Advanced Breast Cancer Patients
Trastuzumab deruxtecan (T-DXd)	ADC, consisting of Trastuzumab, a HER2-specific antibody, and Deruxtecan, a DNA cross-linking agent, is capable of delivering Deruxtecan to tumor cells via HER2-mediated endocytosis, leading to tumor cell death.	HER2	Marketed	Significantly improved objective remission rates and progression-free survival compared with other treatment options in HER2-positive patients with advanced breast cancer, but also increased the risk of moderate or severe interstitial lung disease
Sacituzumab govitecan (S-G)	ADC, consisting of Sacituzumab, a Trop-2 specific antibody, and Govitecan, a topoisomerase I inhibitor, inhibits DNA replication and transcription in tumor cells by delivering Govitecan into tumor cells via Trop-2-mediated endocytosis.	Trop-2	Marketed	Significantly improved objective remission rates and overall survival compared to other treatment regimens in patients with TNBC, but also increased moderate or severe hematologic and non-hematologic toxicity

HER2-Targeted ADCs: Clinical Implications and Future Directions

T-DM1 and T-DXd have set new benchmarks in the management of HER2-positive breast cancer, offering superior efficacy and safety compared to traditional chemotherapy regimens. T-DM1 has become a cornerstone in the treatment of HER2-positive breast cancer, particularly in the second- or third-line setting, with clinical trials demonstrating significant improvements in progression-free survival (PFS) and overall survival (OS).[65,66] The combination of T-DM1 with other targeted agents, such as tucatinib, also shows promise in enhancing therapeutic outcomes.[67]

T-DXd, with its higher drug-to-antibody ratio and more potent cytotoxic payload, has further expanded the therapeutic potential for HER2-positive breast cancer. Clinical trials like DESTINY-Breast01 have underscored its superiority over existing treatments, positioning T-DXd as a preferred option for patients who have exhausted other therapies.[68] Ongoing research is exploring the utility of T-DXd in earlier lines of therapy and in combination with immunotherapeutic agents to enhance its efficacy and tackle resistance mechanisms.[9]

Trop-2-Targeted ADCs: Clinical Impact and Research Directions

SG has demonstrated significant clinical benefits in patients with metastatic TNBC, a subgroup that traditionally has limited treatment options and poor outcomes. The ASCENT trial highlighted SG's potential, showing substantial improvements in PFS and OS compared to standard chemotherapy.[69] The higher objective response rate (ORR) and manageable safety profile of SG underscore its therapeutic advantage, making it a pivotal addition to the TNBC treatment arsenal.[70]

Future research on Trop-2-targeted ADCs is focused on addressing challenges such as resistance development, drug-linker stability, and off-target effects. Strategies to overcome these obstacles include optimizing linker chemistry to enhance drug stability and release, as well as combining ADCs with other therapeutic modalities, such as immune checkpoint inhibitors, to potentiate antitumor activity.[59] Expanding the application of Trop-2-targeted ADCs to other Trop-2 expressing tumors and exploring their use in earlier lines of therapy are also key areas of investigation, potentially broadening the impact of this therapeutic approach.[71]

The advent of ADCs targeting HER2 and Trop-2 marks a paradigm shift in the treatment of aggressive breast cancer subtypes. These innovative therapies offer a tailored approach that maximizes therapeutic efficacy while minimizing systemic toxicity, addressing the heterogeneity and resistance challenges inherent in breast cancer. Continuous research and clinical trials are essential to optimize these therapies, explore combination strategies, and extend their application to a broader range of cancers, ultimately improving patient outcomes and advancing the field of oncology.

Disclosure

The authors report no conflicts of interest in this work.

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