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REVIEW

Advances in Immunotherapy for HER2 Low-Expressing Triple-Negative Breast Cancer

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Abstract: Triple-negative breast cancer (TNBC) is highly malignant with poor prognosis, and immune checkpoint inhibitors (ICIs) provide only limited survival benefits. A key emerging subtype is HER2 low-expressing TNBC, where HER2 expression influences immune microenvironment, clinical behavior, and therapeutic response. Antibody-drug conjugates (ADCs), particularly trastuzumab deruxtecan (T-DXd), have markedly improved survival and also exert antitumor effects through immune activation. Preclinical data suggest synergy when T-DXd is combined with ICIs. However, HER2-low TNBC often has an immune-suppressive microenvironment, underscoring the need for additional strategies. Tumor vaccines and genomics-driven targeted drugs, such as trastuzumab–α-amanitin conjugates, hold promise in reactivating antitumor immunity. This review summarizes current progress in immunotherapy for HER2 low-expressing TNBC, with emphasis on ADCs, combination regimens, and emerging precision strategies, aiming to inform future research and clinical application.

Keywords: T-DXd, antibody-drug conjugate, immune microenvironment, combination therapy, treatment resistance

Introduction

Breast cancer is the most common cancer in women around the world, accounting for approximately 11.7% of new cancer cases in 2020 and becoming a leading cause of death among women.[1,2] TNBC accounts for 15–20% of breast cancer cases,[3] and there are varying degrees of HER2 protein expression in TNBC. In Asian women, HER2-low expressing TNBC accounts for 47.72% of all patients with this subtype,[4] whereas this proportion is approximately 32% in Western populations.[5] HER2 expression influences breast cancer treatment not only through the bystander effect of anti-HER2 ADCs but also due to its instability between primary and metastatic lesions.[6,7] As one of the pathways for tumor cell proliferation, HER2 protein expression levels theoretically affect the efficacy and prognosis of TNBC.[8] The application of ICIs in TNBC has improved efficacy and prognosis,[9] yet survival remains unsatisfactory. Current research efforts are predominantly centered on the therapeutic effects of immune checkpoint inhibitors in TNBC or HER2-positive breast cancer;[10] however, the efficacy of immunotherapy in the HER2-low expressing TNBC subgroup remains inadequately investigated. In patients with TNBC receiving neoadjuvant chemotherapy, no significant differences in clinical characteristics or prognosis were observed between the HER2-low and HER2-negative subgroups,[11] suggesting that the mechanistic influence of HER2-low expression on treatment outcomes in this subtype may be complex. Furthermore, while monotherapy with PD-1/PD-L1 inhibitors demonstrates suboptimal efficacy, combination regimens incorporating chemotherapy, targeted therapy, or radiotherapy have shown superior treatment outcomes.[12,13] We should look into whether different levels of HER2 expression affect how well immunotherapy works for TNBC and whether combination regimens based on ICIs improve prognosis in HER2 low-expressing TNBC.

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Definition and Clinical Characteristics of HER2 Low-Expressing Breast Cancer

HER2 is a key biological marker in breast cancer and a member of the ERBB family of tyrosine kinase receptors. It is a transmembrane protein with tyrosine protein kinase activity, composed of an extracellular ligand-binding domain, a single-chain transmembrane domain, and an intracellular protein tyrosine kinase domain.[14] HER2 protein expression is categorized into IHC 0, 1+, 2+, and 3+, with IHC 3+ indicating HER2 overexpression or equivalent to HER2 gene amplification, while IHC 1+ and 2+ expression (FISH negative) is classified as HER2 low expression.[15,16] Thanks to better detection technology, we now know that some IHC 0 cases have very low level of HER2 protein expression, specifically IHC <1+ but >0. Since the treatment for breast cancer with extremely low HER2 expression may differ from that of individuals with no HER2 expression, the concept of HER2-ultrazero has been introduced.[17]

HER2 low expression accounts for 67% of the breast cancer population,[18] potentially involving molecular subtypes including Luminal A, Luminal B1, and triple-negative, with HER2 low expression accounting for 45–55% of TNBC.[19] Currently, hormone receptor (HR) positive breast cancer has shown good responses to drug therapy; however, after multiple lines of treatment, HR positive breast cancer may also transform into TNBC.

Clinically, compared to HER2 IHC 0, HER2 low expressers exhibit more aggressive clinical features: larger tumors, more lymph node involvement, higher histological grades, higher Ki67 values, and poorer prognoses. Kaplan-Meier analysis shows that, relatively speaking, patients with HER2 low-expressing TNBC have shorter overall survival. Clinical manifestations of HER2 low-expressing breast cancer may be closer to those of HER2 positive breast cancer.[20,21]

Currently, the treatment of TNBC does not significantly differentiate based on HER2 expression levels, and the survival rates for TNBC are lower than for other types of breast cancer,[22] failing to achieve the long-term survival goals for breast cancer as a chronic disease. As mentioned earlier, TNBC is not entirely devoid of therapeutic targets; fully exploring the role of HER2 in the tumor cell proliferation pathway and identifying intervenable targets may further enrich treatment options for TNBC.

Immune Microenvironment Characteristics of HER2 Low-Expressing TNBC

The unique immune environment is crucial for immunotherapy in TNBC, and there are clear differences in the immune microenvironment between HER2 IHC 0 and low-expressing cases. Single-cell RNA sequencing[20] shows that HER2 IHC 0 TNBC has a more active immune microenvironment compared to HER2 low-expressing TNBC, with higher expression of immunoglobulin-related genes (IGHG1, IGHG4, IGKC, IGLC2) and T cell receptors, more macrophage polarization, and CD8+ effector T cell infiltration, as well as higher levels of immune therapy target markers; HER2 low-expressing TNBC exhibits a more aggressive invasive phenotype.

Tumor-infiltrating lymphocytes (TILs) are a population of lymphocytes that infiltrate tumor tissue, and TILs levels have a certain predictive pattern for prognosis in different molecular subtypes of breast cancer. Among all breast cancer subtypes, TILs levels are significantly positively correlated with the pathological complete response rate after neoadjuvant chemotherapy.[23–25] Based on this, the breast cancer diagnosis and treatment guidelines of Chinese Society of Clinical Oncology (CSCO) 2022 included stromal TILs (sTILs) as one of the recommended pathological detection items.[26] For TNBC, higher levels of TILs correlate with better prognosis.[27,28] Inspired by the good efficacy of T-DXd in HER2 low-expressing breast cancer, some studies[29] have explored the relationship between HER2 low expression and sTILs in TNBC patients, showing no significant association between HER2 low expression and sTILs density or response to neoadjuvant chemotherapy, suggesting a complex relationship between HER2 expression levels and tumor immunity.

Immune Response Mediated by T-DXd: Breakthroughs and Challenges

TNBC has a high rate of recurrence and metastasis, with few treatment options and a tendency for drug resistance. T-DXd is a new type of ADC that targets HER2, composed of a humanized anti-HER2 IgG1 monoclonal antibody and a topoisomerase I inhibitor DXd (deruxtecan) linked by a cleavable peptide-based linker. It has structural and mechanistic

advantages, with the antibody portion retaining the biological activity of trastuzumab and maintaining affinity for HER2 after drug conjugation, while its antibody-dependent cell-mediated cytotoxicity (ADCC) is unaffected, and the immune response involving the T-DXd antibody portion participates in the antitumor process. The DESTINY-Breast04 study[30] was the first randomized controlled Phase 3 trial of T-DXd for HER2 low-expressing breast cancer, where participants received T-DXd or physician's choice of chemotherapy. In the HR-negative breast cancer cohort, the median progression-free survival (mPFS) for the T-DXd group was 8.5 months, compared to 2.9 months for the physician's choice chemotherapy group (hazard ratio 0.46), indicating a 54% reduction in the risk of disease progression; the median overall survival (mOS) for the T-DXd group was 18.2 months, compared to 8.3 months for the physician's choice chemotherapy group (hazard ratio 0.48), indicating a 52% reduction in the risk of death. Among ITT (intention-to-treat) patients, 12.1% of those receiving T-DXd experienced drug-related interstitial lung disease or non-infectious pneumonia. T-DXd's strong ability to target HER2 goes even further. The DESTINY-Breast06 study[31] primarily evaluated the efficacy and safety of T-DXd versus physician's choice of chemotherapy for HR+, HER2 low-expressing or HER2-ultralow advanced breast cancer, showing a trend of benefit in the HER2-ultralow population (mPFS 13.2 months vs 8.3 months, HR 0.78), indicating that even with weak HER2 expression in tumor cells, T-DXd may still effectively identify targets.

Li-Chung Tsao and colleagues[32] further explored the relationship between the unique structure of T-DXd and immune activation, finding that the effects of T-DXd on HER2 low-expressing and non-expressing breast cancer do not depend on HER2 binding and ADC internalization, but rather rely on extracellular cathepsin L (CTSL). CTSL is widely expressed in tumor cells and stroma, independent of HER2 status. Extracellular CTSL requires low pH activation, specifically cleaving the T-DXd linker to promote effective payload release and induce cytotoxicity against tumor cells. The DXd payload induces strong immunogenic cell death (ICD), activating myeloid antigen-presenting cells, enhancing antigen presentation capacity, and chemokine secretion. The cytotoxicity of the DXd payload and the immune activation effects it mediates form a dual antitumor mechanism of "direct killing-immune activation". On the other hand, DXd significantly upregulates CD47 (cluster of differentiation 47) expression in HER2 positive breast cancer cells, inhibiting antibody-dependent cellular phagocytosis (ADCP). Studies have also found that combining T-DXd with CD47 blockers can synergistically enhance innate immune activation and adaptive T cell responses, inducing durable CD8+ T cell memory to prevent tumor recurrence (Figure 1).

T-DXd possesses a triple mechanism of action targeting, chemotherapy, and immunotherapy, greatly improving survival data for HER2-expressing patients and representing another significant breakthrough beyond TNBC immunotherapy. However, T-DXd faces a short survival period after developing resistance. Professor Paolo Tarantino's team[33] conducted in-depth research on this issue, revealing that after T-DXd treatment, subsequent treatment for HER2+, HR+/HER2-, and HR-/HER2- patients resulted in real-world progression-free survival (rwPFS) of 4.3 months, 3.0 months, and 2.7 months, respectively, with mOS of 12.6 months, 8.1 months, and 4.8 months, further highlighting the severe clinical challenges faced by TNBC. How to delay resistance during the T-DXd treatment Phase Is a current research focus. Another preclinical study[34] showed that in mouse models, the combination of T-DXd and anti-PD1 (programmed cell death 1) antibody was more effective than monotherapy, possibly related to increased T cell activity and T-DXd-induced upregulation of PD-L1 (programmed cell death-ligand 1) expression. Currently, clinical studies on T-DXd combined with ICIs for breast cancer are still in the early stages. The DS8201-A-U105 study[35] is a phase Ib clinical trial showing that T-DXd combined with nivolumab has comparable antitumor activity in HER2-expressing (IHC 0–3+) breast cancer to T-DXd monotherapy, but the proportion of HER2 low-expressing patients is low, and most are HR positive, making it difficult to explain efficacy in TNBC. Additionally, adverse reactions after the combination of the two drugs cannot be ignored. Tras-DXd-MTL1 is a novel ADC that integrates the topoisomerase I inhibitor DXd with a Toll-like receptor 7 (TLR7) agonist, MTT5. It retains the DNA-damaging and cytotoxic properties of DXd, while MTT5 promotes immune cell infiltration and activates dendritic cells and CD8+ T cells, thereby enhancing the immune response within the tumor microenvironment. Animal studies have demonstrated that Tras-DXd-MTL1 exhibits significantly superior efficacy in inhibiting the growth of trastuzumab-resistant JIMT-1 tumors with moderate HER2 expression (equivalent to IHC 1+ to 2+) compared to T-DXd.[36] Consequently, Tras-DXd-MTL1 holds promising therapeutic potential for patients with HER2-low breast cancer.

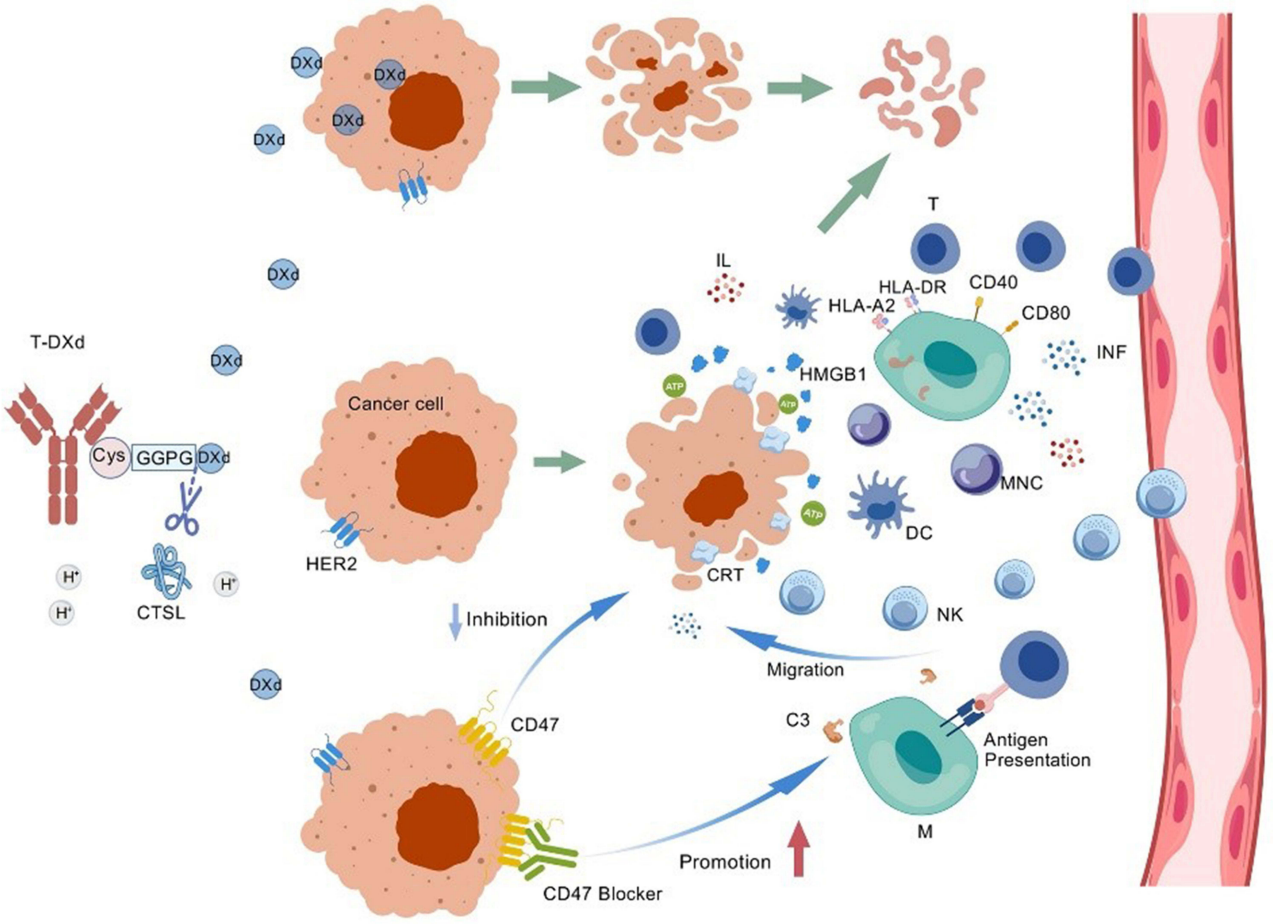

Figure 1 DXd Payload Release from T-DXd Induces Cytotoxicity and Immunogenic Cell Death in the Tumor Microenvironment. In a low pH extracellular mat rix, cathepsin L is activated, specifically cuts the four peptide linkers (GGFG) of T-DXd, which releases the potent DXd payload. DXd has cytotoxic effects on breast cancer cells and promotes apoptosis; it also induces immunogenic cell death (ICD), causes DNA damage, and releases eATP, high mobility group protein B1, and calreticulin, activating dendritic cells, macrophages, and monocytes, and enhancing their ability to present antigens, like upregulating the expression of HLA-A2, HLA-DR, and costimulatory molecules CD40 and CD80 in macrophages, and promoting the secretion of chemokines. Furthermore, DXd boosts CD47 expression in HER2-positive breast cancer cells, which inhibits antibody-dependent cellular phagocytosis (ADCP); CD47 blockers can reverse this situation and synergistically enhance innate immunity and adaptive T cell responses.

Abbreviations: CTSL, cathepsin L; CD47, cluster of differentiation 47; IL, interleukin; CRT, calreticulin; C3, complement 3; HMGB1, high mobility group protein B1; HLA-A2, human leukocyte antigen-A2; HLA-DR, human leukocyte antigen-DR; CD40, cluster of differentiation 40; CD80, cluster of differentiation 80; T, T lymphocyte; DC, dendritic cell; NK, natural killer cell; M, macrophage; MNC, mononuclear cell; INF, interferon.

Tumor Vaccine Combination Strategies to Overcome Immune Suppression

Metastatic tumors may have immune suppressive effects,[37] necessitating external intervention to restore the body's antitumor immunity. Tumor vaccines induce tumor-specific immune responses using tumor cell lysates, tumor-associated antigens (TAAs), and tumor peptides. Most tumor vaccines target TAAs to elicit cytotoxic T lymphocyte responses. In breast cancer, the most researched tumor vaccines are HER2-related peptide vaccines, including nelipepimut-S and AE37.[38–41] Unlike conventional dose-response relationships, studies show that HER2 low expressers, particularly those with IHC 1+ status, exhibit stronger immune responses and may derive the greatest clinical benefit from the nelipepimut-S vaccine.[39] Two studies on nelipepimut-S[40] and AE37[41] show that using HER2 peptide vaccines as adjuvant immunization to prevent recurrence in patients with positive lymph nodes or high-risk negative lymph nodes and HER2 expression (IHC 1–3+) did not show significant DFS benefits for the entire population, but possible clinical benefits were observed in the HER2 low-expressing (IHC 1+, 2+) subgroup that included TNBC. However, further mid-term analysis of a Phase III clinical trial[42] on nelipepimut-S did not show vaccine superiority, leading to the study's termination, indicating that

more optimized strategies are needed to harness vaccine effects, such as patient selection, biomarkers, and combination therapies.

Trastuzumab initiates ADCC effects by binding its Fc region to Fcγ receptors III on NK (natural killer) cells, antigen-presenting cells, or immune effector cells. Due to the significantly lower tumor burden and tumor-induced immune suppression in micro-metastatic tumors compared to macro-metastatic tumors, trastuzumab was once considered effective for early breast cancer with low HER2 expression. However, results from large phase III randomized trials[43] showed no benefit from adding trastuzumab as adjuvant therapy for HER2 low-expressing breast cancer, even for patients with HER2 IHC 2+ expression. In a phase IIb trial[44] of nelipepimut-S combined with trastuzumab for high-risk HER2 low-expressing breast cancer, the experimental group received nelipepimut-S + GM-CSF (granulocyte-macrophage colony-stimulating factor) + trastuzumab, while the control group received placebo + trastuzumab. There was no significant difference in 36-month DFS rates between the experimental and control groups in the ITT population, but significant improvements were observed in the TNBC cohort (84.5% vs 70.6%, HR 0.25, P = 0.01) and in HER2 IHC 1+ expressers within the TNBC cohort (94.1% vs 66.9%, HR 0.17, p = 0.01). Neither trastuzumab nor nelipepimut-S alone showed significant benefits, but their combination yielded notable effects, especially in TNBC. Trastuzumab can enhance the response of anti-HER2 CD4+ Th1 cells and the uptake and cross-presentation of HER2 by dendritic cells,[45,46] while nelipepimut-S vaccination increases antigen presentation by dendritic cells and the population of nelipepimut-S specific CD8+ T cells,[47] indicating a synergistic effect in activating tumor immunity (Figure 2). Of course, the significant benefits observed in the TNBC cohort may also be related to increased PD-L1 expression and the inherent immune suppressive microenvironment in TNBC.[48] Additionally, since TNBC does not express ER (estrogen receptor), there is no suppression of MHC I (major histocompatibility complex I) expression by ER, which does not affect T cell activation.[49] Furthermore, the benefits for HER2 IHC 1+ expressers appear more pronounced than for HER2 IHC 2+ expressers, which seems contradictory to the idea that stronger immune responses arise from greater direct immune stimulation, but

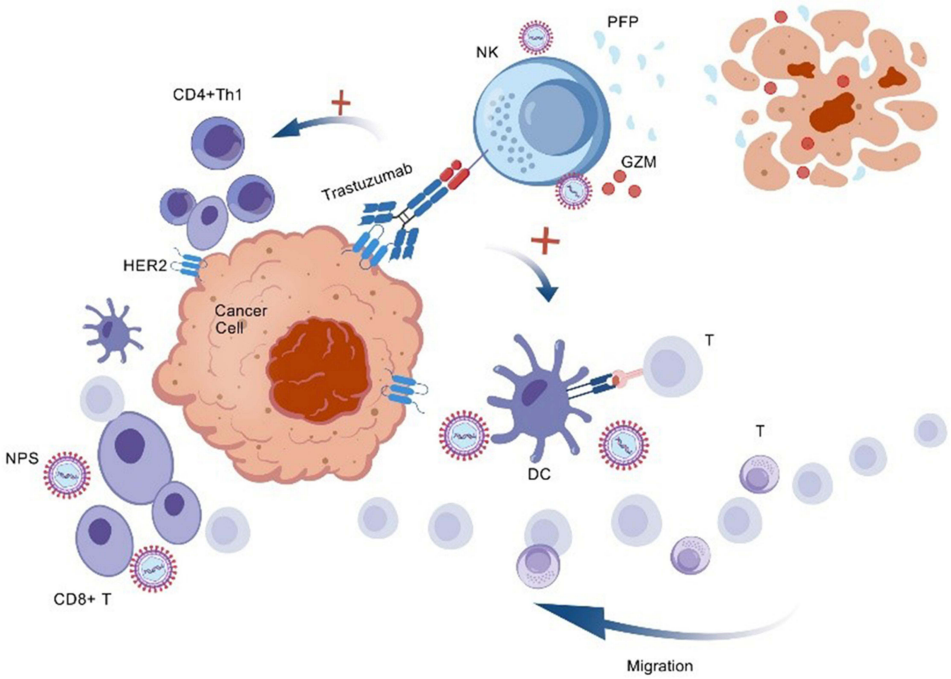

Figure 2 Synergistic Antitumor Immunity of Trastuzumab and Nelipepimut-S. The Fab segment of trastuzumab binds to HER2 on the surface of breast cancer cells, while the Fc segment binds to FcγR on natural killer cells (NK cells), subsequently triggering NK cell activation and the release of perforin and granzyme, leading to the lysis of breast cancer cells. This binding also promotes the infiltration of CD4+ T-helper cell 1 and the antigen presentation by dendritic cells. The administration of nelipepimut-S directly promotes antigen presentation by dendritic cells, while also increasing the infiltration of nelipepimut-specific CD8+ T lymphocyte. Both exert immune synergistic effects through a complex immune network.

Abbreviations: NPS, nelipepimut-S; CD4+ Th1, CD4+ T-helper cell 1; CD8+ T, CD8+ T lymphocyte; NK, natural killer cell; DC, dendritic cell; T, T lymphocyte; PFP, perforin; GZM, granzyme.

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repeated and intense exposure to immunogenic peptides may lead to immune exhaustion or non-responsiveness, reducing the efficacy of peptide vaccines.[50,51] This also illustrates the complexity of the field from another perspective. The HER2-low expression population may harbor finer biological heterogeneity, which poses challenges for future treatment strategies and biomarker development.

Novel Targeted-Immunotherapy: Genomics-Driven Strategies

Cancer genomic analyses indicate that heterozygous deletions on chromosome 17p are a common genetic phenomenon in various human cancers.[52,53] Analysis of the TCGA (the cancer genome atlas) breast cancer dataset shows that 32.2% of HER2 low-expressing (HER2 1+ and 2+) TNBC patients have 17p heterozygous deletions.[54] The POLR2A gene is located in the 17p chromosomal region and is primarily responsible for encoding the catalytic subunit of RNA polymerase II (RNAP2) complex.[52] Since RNAP2 is responsible for mRNA synthesis, which is essential for cell survival, complete suppression of the POLR2A gene is lethal to any type of cell. α-Amanitin is a bicyclic octapeptide toxin that can specifically bind to eukaryotic RNAP2 due to its unique chemical structure.[55] Heterozygous deletions on chromosome 17p lead to reduced POLR2A expression and decreased RNAP2 synthesis, significantly increasing cancer cells' sensitivity to α-Amanitin. Researchers have successfully developed a novel ADC drug, T-Ama, by conjugating α-Amanitin with trastuzumab for treating HER2 low-expressing breast cancer, especially TNBC. Studies show that T-Ama treatment inhibits the growth of tumors in mice with 17p heterozygous deletions/HER2 low expression and prolongs survival. Immune activity of α-Amanitin was also observed in T-Ama, including the induction of type I interferon and interferon-stimulated genes (MX1, OAS2, and RSAD2).[54] Research confirms that for HER2 low-expressing breast cancer with 17p heterozygous deletions, monotherapy with PD-1 antibodies has minimal antitumor activity, but T-Ama monotherapy significantly inhibits tumor growth. However, the combination of T-Ama with PD-1 antibodies demonstrates even stronger anticancer activity.[54] CyTOF (cytometry by time-of-flight) analysis shows that T-Ama monotherapy or in combination with PD-1 antibodies enhances immune cell infiltration, particularly CD8+ T effector cells and conventional CD4+ T cells, indicating that the treatment promotes an antitumor immune microenvironment.[54] Therefore, breakthroughs in treating HER2 low-expressing breast cancer could delve deeper into driving genomic features to design novel drugs with both precise targeting and immune modulation functions, actively exploring their synergistic combinations with immunotherapy to achieve precision-targeted immune combination therapy based on genomic characteristics.[56]

Challenges and Controversies

Although clinical and preclinical researches on immunotherapy for HER2 low-expressing TNBC is expanding and has achieved notable advancements (Table 1), clinical translation still faces severe challenges. The primary issue is the high heterogeneity of this population,[57] with significant differences in immune microenvironment characteristics based on varying levels of HER2 expression, complicating the construction of efficacy prediction models. Although the core drug T-DXd significantly improves survival, the 12.1% incidence of interstitial pneumonia severely restricts long-term medication safety;[30] more critically, the mOS for patients after T-DXd resistance is only 4.8 months,[33] far lower than for other subtypes, highlighting the urgency of unraveling resistance mechanisms. Emerging genomics-driven strategies like T-Ama (targeting 17p deletions) show synergistic immune activation effects but only cover 32.2% of cases with specific genomic alterations and are currently still in preclinical research stages. There are also contradictions in the field of combination therapies; while trastuzumab combined with the nelipepimut-S vaccine significantly improved the 3-year DFS rate to 94.1% in HER2 IHC 1+ TNBC, there was no significant improvement for IHC 2+ patients.[44] Preclinical studies suggest that T-DXd can enhance PD-L1 expression and promote T cell infiltration,[34] yet clinical research data supporting its synergistic effects with PD-1 inhibitors is still lacking.

Conclusion

Immunotherapy for HER2 low-expressing TNBC has progressed beyond theoretical promise to deliver tangible clinical benefits, exemplified by the survival improvements with T-DXd. However, pressing challenges—including tumor heterogeneity, treatment-related toxicity, and acquired resistance—remain unresolved. Future research should prioritize elucidating

Table 1 Clinical and Preclinical Research Studies on Immunotherapy for HER2-Low-Expressing TNBC That Have Been Conducted

No.	Study Intervention/Arm	Study Type	Subject Population/ Model	HER2 Expression Level	Target(s)	Primary Outcomes	Main Adverse Events/ Toxicities	Remarks/ Notes
1	T-DXd vs Physician's Choice of hemotherapy[30]	Phase III Clinical Trial	Pretreated patients with HER2-low metastatic breast cancer	HER2 IHC 1+ or IHC 2+/ISH-	HER2 protein	TNBC Subgroup mPFS: 8.5m vs 2.9m (HR 0.46); mOS: 18.2m vs 8.3 m (HR 0.48)	Interstitial neumonitis	
2	T-DXd + CD47 Blocker vs T-DXd vs CD47 Blocker vs Control (Rituximab)[32]	Animal Study (Preclinical)	HER2A16 transgenic mouse model	HER2-high expression (some 2+ expression)	HER2 protein, CD47-SIRPα axis	T-DXd + CD47 Blocker: 60% of treated mice achieved complete tumor regression and long-term survival; T-DXd: prolonged survival but limited complete regression; CD47 Blocker/Control: limited efficacy		
3	T-DXd + anti-PD vs T-DXd vs anti-PD-1[34]	Animal Study (Preclinical)	BALB/c mice inoculated with CT26.WT-hHER2 cells	HER2-high expression (some 2+ expression)	HER2 protein, PD-1 protein	Complete Response Rate: 65% vs 20% vs 10%; Survival Rate at Day 38: 80% vs 20% vs 20%		
4	E75 + GM-CSF vs Control (No treatment)[40]	Phase I/II Clinical Trial	Breast cancer patients with node-positive or high-risk node-negative disease who completed standard adjuvant therapy	HER2 IHC 1+, 2+, or 3+	HER2 protein	HER2-low Subgroup 5-year DFS: 88.1% vs 77.5% (difference 10.6%, P=0.16)	Injection site erythema/ pruritus, bone pain, flu-like symptoms, fatigue, delayed urticaria (Grade 1–2)	Related trials: NCT00841399, NCT00584789
5	AE37 + GM-CSF vs GM-CSF[41]	Phase II Clinical Trial	Breast cancer patients with node-positive or high-risk node-negative disease, enrolled within 1–6 months after standard adjuvant therapy	HER2 IHC 1+, 2+, or 3+	HER2 protein	HER2-low TNBC Subgroup 5-year DFS: 77.7% vs 49.0% (P=0.12, HR 0.403)	Injection site erythema/ pruritus, bone pain, flu-like symptoms, fatigue (Grade 1–2)	Related trial: NCT00524277

(*Continued*)

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Table 1 (Continued).

No.	Study Intervention/Arm	Study Type	Subject Population/ Model	HER2 Expression Level	Target(s)	Primary Outcomes	Main Adverse Events/ Toxicities	Remarks/ Notes
6	NPS + GM-CSF + Trastuzumab vs Placebo + GM-CSF + Trastuzumab[44]	Phase IIb Clinical Trial	Patients with node-positive and/or triple-negative, HER2-low invasive breast cancer who completed standard adjuvant therapy	HER2 IHC 1+ or 2+, FISH non-amplified	HER2 protein	TNBC Subgroup 36-month DFS: 84.5% vs 70.6% (P=0.01, HR 0.25); HER2 IHC 1+ TNBC Subgroup 36-month DFS: 94.1% vs 66.9% (p=0.01, HR 0.17)	Injection site reactions, flu-like symptoms, decreased left ventricular ejection fraction	Related trial: NCT01570036
7	T-Ama + anti-PD-1 vs T-Ama vs anti-PD-1 vs Control (Trastuzumab)[54]	Animal Study (Preclinical)	C57BL/6-Tg (WapHER2) transgenic mice implanted with E0771 (HER2-low / 11B-loss) cells	Equivalent to HER2 IHC 1+	HER2 protein, RNA polymerase II, PD-1 protein	Median Survival: T-Ama + anti-PD-1 significantly longer than other groups, followed by T-Ama; anti-PD-1 and Control were comparable		
8	Tras-DXd-MTL1 vs T-DXd vs Trastuzumab[36]	Animal Study (Preclinical)	SCID-beige immunodeficient mice implanted with JIMT-1 cells	Equivalent to HER2 IHC 1+ or 2+	HER2 protein, TLR7	Inhibitory effect on trastuzumab-resistant JIMT-1 tumors: T-DXd-MTL1 > T-DXd > Trastuzumab		

Abbreviations: IHC, immunohistochemistry; PFS, progression-free survival; HR, hazard ratio; OS, overall survival; GM-CSF, granulocyte-macrophage colonystimulating factor.

the mechanisms underlying T-DXd resistance, as overcoming this resistance could meaningfully extend patient survival; for example, reversing resistance may raise median overall survival beyond the current 4.8 months observed after T-DXd failure in advanced TNBC. In parallel, strategies aimed at reactivating antitumor immunity—such as cancer vaccines combined with monoclonal antibodies—warrant further optimization in selected subpopulations. The development of novel, lower-toxicity ADCs and genomics-informed drug candidates like T-Ama highlights a new direction for precision-targeted immunotherapy. Moving forward, combining molecular stratification with rationally designed treatment regimens will be essential to maximize therapeutic efficacy while minimizing adverse events. Collectively, these advances are steering the management of HER2-low TNBC toward an integrated "genomic-immune precision medicine" paradigm, in which therapy is tailored not only to HER2 expression level but also to intrinsic genomic features and the individual's immune contexture.

Data Sharing Statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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