

Challenges and Possible Treatments for HER2-associated Breast Cancer

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ABSTRACT: Globally, breast cancer is the most common type of cancer in women. Human epidermal growth factor receptor 2 (HER2) overexpression is a significant cause of breast cancer. Breast cancer is categorized into different subtypes according to the level of HER2 expression. This categorization ensures the most efficient treatment is given to every patient. HER2-low breast cancer (BC) is a novel subtype that has been discovered. With fewer HER2 proteins detected, many treatments and former anti-drug conjugates (ADCs) are not useful in curing these patients. Nevertheless, several clinical trials have shown that trastuzumab deruxtecan (T-DXd), a type of ADC, is helpful in the treatment of HER2-low BC cases. This review aims to distinguish different subtypes of breast cancer, treatments available, the mechanism and efficacy of trastuzumab deruxtecan, and identify current challenges and future potential in breast cancer treatment.

KEYWORDS: Medical and Health Sciences, Pharmaceutical Sciences, HER2 Breast Cancer, HER2-Low, Trastuzumab Deruxtecan.

■ Introduction

In 2025, an estimated 319,750 women were diagnosed with breast cancer.¹ This is not only happening in the US, but it is a worldwide issue. Breast cancer is common in women between the ages of 50 and 69, who have inherited cancer mutations, poor health status like obesity, habits like smoking and drinking alcohol, and experience of radiation exposure or hormone replacement therapy.² These will all cause breast cancer to develop when cancer cells abnormally multiply and eventually create a tumor in the breast.

Human epidermal growth factor receptor 2 (HER2), estrogen receptor (ER), and progesterone receptor (PR) are proteins that are deeply associated with breast cancer. HER2, estrogens, and progesterone all help cancerous cells grow. The status of the receptors' expression creates different subtypes of breast cancer that require different treatments. ER-positive (ER+) tumors have estrogen receptors; PR-positive (PR+) tumors have progesterone receptors; and HR-positive (HR+) tumors have both. Another way to categorize breast cancer types is by measuring the amount of HER2 protein. They can be categorized into HER2-positive and HER2-negative. HER2-negative includes HER2-low and HER2-zero.

Anti-HER2 targeting agents have been used in HER2-positive cases and have proved to be helpful.² Common anti-HER2 drugs include trastuzumab, pertuzumab, trastuzumab deruxtecan, and trastuzumab.³ HER2-negative tumors receive endocrine therapies, chemotherapies, or other treatments, depending on the positivity of ER and PR. HER2-low breast cancer is a refined category within HER2-negative. About 60% of HER2-negative tumors are categorized as HER2-low, with a small amount of HER2 but not entirely without expression.⁴

Despite traditional treatments, discoveries in new treatments shed light on the field of research. HER2-targeting

drugs were never thought to be effective in HER2-low cases with low HER2 expression. Recent studies have proved that trastuzumab deruxtecan (T-DXd), a type of antibody drug conjugate (ADC), has shown remarkable progress in stopping breast cancer progression and extending patients' survival span. Adaptation of T-DXd can provide a more efficient HER2-low BC treatment, benefiting those who used to be categorized as HER2-negative. This review will introduce different types of HER2-associated breast cancer, current treatment for each of them, and challenges and future potential of breast cancer therapies. This review aims to provide a clear overview of evolving clinical data and treatments surrounding HER2-associated breast cancer, challenges, and possible solutions.

■ Discussion

1. Types of HER2-associated Breast Cancer: HER2-positive, HER2-low, HER2-zero:

Breast cancer is a heterogeneous disease, or a disease that has more than one cause. In breast cancer tumors, HER2 expression can be the cause of the abnormal growth of cancerous cells. Figure 1 illustrates the HER2 signaling pathway. HER2 receptors do not have a known ligand. Instead, it is activated through dimerization with other receptors from the family, HER3, HER4, or itself, HER2. Overexpression of the HER2 receptor proteins switches on permanent dimerization and activation. Several types of amino acid mutations were also found to be responsible for triggering dimerization of HER-family receptors.⁶ Even when growth factors are absent, HER2 dimers keep signaling. Thus, cells bypass normal checkpoints easily, resist apoptosis, and proliferate excessively. This uncontrollable cell growth leads to the formation of tumors. According to the status of HER2 expression, breast cancer can be divided into

different types: HER2-positive, HER2-low, and HER2-zero. Immunohistochemistry (IHC) and in situ hybridization (ISH) are two methods that are used to distinguish the distinct subtypes. This process is important because patients of different types respond positively to different treatments. The next section will introduce the methods to identify them and the current treatment available.

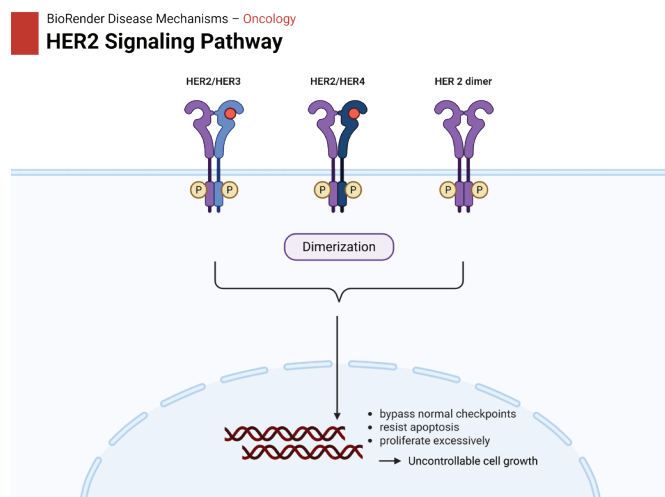


Figure 1: HER2 Signaling Pathway in Breast Cancer. When the HER2 protein undergoes homodimerization (HER2 dimerizes with HER2) or heterodimerization (HER2 dimerizes with other receptor proteins in the family), it triggers uncontrollable cell growth by allowing the tumor cell to bypass normal checkpoints, resist apoptosis, and proliferate excessively. (Created in <https://BioRender.com>)

1.1. Methods Used to Distinguish HER2 Breast Cancer Subtypes:

To distinguish different types of HER2 breast cancer, IHC analysis is usually conducted first, and ISH is later used to further identify the amount of expression. IHC staining is a staining method that detects and visualizes specific proteins we are looking for. The IHC score ranges from 0, 1+, 2+, to 3+ depending on the amount of visible staining in the cells. Figure 2 shows how HER2 expression can be visualized on IHC staining results. A higher score represents more expression.

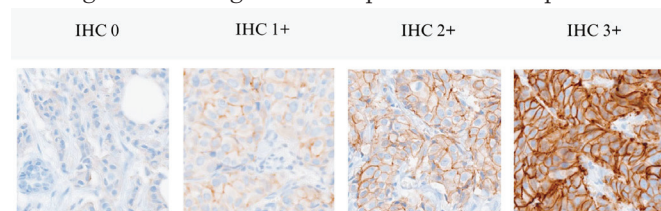


Figure 2: IHC Score With Visualized Results.⁵ Tumor cells with higher HER2 expression are presented with a darker color and higher density on the IHC staining results.

In breast cancer tumors, the amount of staining of the HER2 protein is the evaluation standard of IHC scores. IHC 3+ has the most obvious HER2 protein expression, and IHC 0 has the least.⁶ Additionally, tumors with an IHC score of 2+ have to take an ISH test to confirm their classification as either HER2-positive or HER2-low. Unlike IHC, ISH aims to test the amplification of the HER2 gene. ISH positive identifies the overexpression of the HER2 gene. Tumors with IHC 3+ or

IHC 2+ with an ISH positive are considered HER2-positive tumors. Tumors with IHC 1+ or IHC 2+ with an ISH negative are considered HER2-low. Lastly, tumors with IHC 0 are diagnosed as HER2-zero. Table 1 shows the clearer version that demonstrates the evaluations.

Table 1: HER2 Breast Cancer Subtypes Evaluations.

HER2 BC Subtype	IHC score (0, 1+, 2+, 3+)	ISH result (positive/negative/not required)
HER2-positive	3+	Not required
	2+	Positive
HER2-low	2+	Negative
	1+	Not required
HER2-zero	0	Not required

1.2. Available Treatments for HER2-positive Breast Cancer: Comparison:

Among all breast cancers, 15-20% are HER2-positive tumors.⁷ These cases with overexpression and amplification of HER2 have a worse prognosis and a high recurrence rate. Fortunately, anti-HER2 therapies have created new and more advanced treatment options for patients with HER2-positive breast cancer. Currently, trastuzumab and pertuzumab are used in first-line treatment, and trastuzumab emtansine and trastuzumab deruxtecan (T-DXd) in second-line treatment.³ Trastuzumab is a type of humanized monoclonal antibody that binds to HER2 receptors to down-regulate the pathway. It binds to three specific regions of domain IV of the HER2 extracellular domain.⁸ Although the efficacy of trastuzumab treatment is shown to be controversial among different study trials regarding treatment duration and whether the tumor is ligand-dependent or ligand-independent, findings suggest that trastuzumab inhibits the cell cycle of tumor cells through suppressing downstream pathways.⁸ For instance, the H0648g phase 3 study significantly proved the effectiveness of trastuzumab. This clinical trial compared the effectiveness of treatment with chemotherapy only and with both trastuzumab and chemotherapy.⁹ 469 patients with HER2-positive metastatic breast cancer were involved in the study, where 234 patients received chemotherapy alone, and 235 patients received chemotherapy combined with trastuzumab. The results of the study show that the addition of trastuzumab to chemotherapy contributed to a significantly longer time to disease progression, longer duration of response, a higher rate of objective response, and a lower rate of death. Trastuzumab was approved by the U.S. Food & Drug Administration (FDA) in 1998 for HER2-positive metastatic breast cancer.

Additionally, another study compared the effectiveness and safety of the drugs used in second-line treatment, trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd).¹⁰ 524 patients with HER2-positive tumors were randomly assigned to receive either trastuzumab emtansine or trastuzumab deruxtecan. The result shows that patients treated with trastuzumab deruxtecan have a higher possibility of survival, survival without disease progression, and a higher rate of objective response. Thus, trastuzumab deruxtecan has been proven to be

superior to trastuzumab emtansine in the second-line treatment. This is mainly due to the higher drug-to-antibody ratio of approximately 8 deruxtecan released after the binding of the drug to HER2 receptors. However, trastuzumab deruxtecan is also associated with side effects, especially interstitial lung disease or pneumonitis.

The other group, the HER2-negative tumors, can receive endocrine therapies. HER2-negative treatments depend on the expression of other proteins involved in the cancer. For example, if estrogen is high in the breast cancer tumor, patients can take drugs that lower the estrogen level or block the receptor.

2. HER2-low Breast Cancer and Trastuzumab Deruxtecan:

HER2-low breast cancer is a new category established from the HER2-negative subtype. HER2-low breast cancer tumors have a lower amount of HER2 protein expression compared to HER2-positive tumors; however, they have more than HER2-zero tumors. Before the discovery of trastuzumab deruxtecan, the amount of HER2 protein wasn't enough for other HER2-targeting drugs to detect. Therefore, HER2-low tumors were treated as HER2-negative tumors, mostly receiving endocrine therapies. Currently, HER2-low tumors are defined by IHC 1+ or 2+ with ISH negativity, and about 60% of HER2-negative tumors are now considered HER2-low. The following section will introduce the characteristics of HER2-low tumors and compare T-DXd with other therapies.

HER2-low tumors are more common in HR-positive than in HR-negative tumors compared to HER2-zero.¹¹ HR-positive tumors are those that overexpress both estrogen and progesterone receptors. This creates the opportunity for a positive response to endocrine therapies targeting the expressed hormones. HER2-low tumors were also proven to have a better prognosis than HER2-zero tumors.¹²

Trastuzumab deruxtecan is an antibody drug conjugate (ADC) that targets the HER2 receptor protein to block growth signaling and damage the DNA, which leads to apoptosis of tumor cells. This paragraph will discuss the function and mechanism of ADC and trastuzumab deruxtecan. When the HER2 gene is mutated, it uncontrollably produces HER2 receptor proteins that regulate cell growth, repair, and apoptosis. ADCs are the “biological missiles,” composed of a monoclonal antibody and a potent drug. They selectively bind to target proteins efficiently and accurately, making them a rising star in the research of cancer therapies.¹³ Trastuzumab deruxtecan combines trastuzumab, the monoclonal antibody, and deruxtecan, the potent drug. They are chemically linked to each other and are infused into the veins so they can be transported to the proteins they are looking for, in this case, the HER2 receptor. Trastuzumab is like a delivery; it transports the payload, deruxtecan, to the HER2 receptor on the membrane of the tumor cells. Then the complex is ferried into the tumor cells, and the chemical linkage between trastuzumab and deruxtecan breaks. Deruxtecan is a type of topoisomerase I inhibitor. As a weapon carried by trastuzumab, when it is released into the tumor cell, it damages the DNA and leads the cell to apoptosis. Moreover, deruxtecan can easily cross

the membrane, entering and attacking neighboring tumor cells regardless of the amount of target protein (HER2) expression. This bystander effect allows it to become one of the most effective drugs in breast cancer therapies and develops its potential to cure patients with HER2-low breast cancer.^{2,14,15} Figure 3 demonstrates how T-DXd works on tumor cells expressing the HER2 protein.

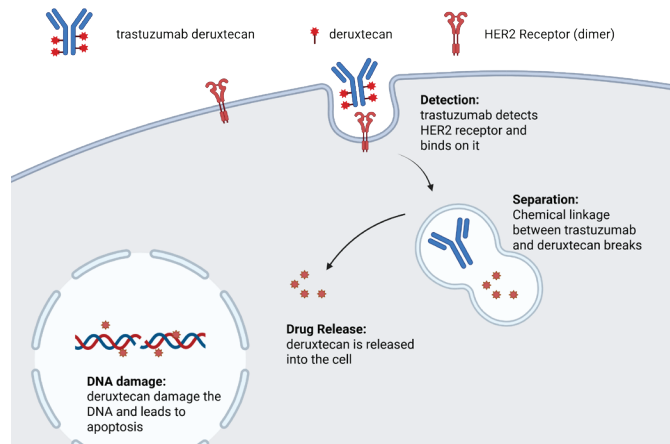


Figure 3: Mechanism of Trastuzumab Deruxtecan. Trastuzumab binds to HER2 receptors and crosses the membrane. After entering the cell, deruxtecan is released to damage DNA, leading to the apoptosis of the tumor cell. (Created in <https://BioRender.com>)

The DESTINY-Breast04 clinical trial proved the effectiveness of T-DXd in HER2-low breast cancer treatment.⁴ 557 patients with HER2-low tumors defined by an IHC 1+ or 2+ with negative results of ISH were involved in this phase III clinical trial.

All of these patients had received one or two chemotherapies before participating in this study. The patients were randomly grouped to compare the T-DXd and standard chemotherapy effectiveness on progression-free survival. The results show that patients treated with T-DXd have significantly longer progression-free survival and overall survival. Thanks to the DB-04 trial, T-DXd became the first approved ADC for use on metastatic HER2-low breast cancer in 2022. This anti-HER2 drug, previously used on HER2-positive tumors, is now developing future potential for ADC treatment in HER2-low and HER2-zero tumors.

3. Challenges and Future Potentials:

New and more advanced drugs and treatments have been developed to target different subtypes of metastatic breast cancer. They establish future potentials based on similar mechanisms, but also face challenges such as the doubtful identification of subtypes, resistance to drugs, and side effects of these drugs. What are the solutions to these issues? What are the future directions of breast cancer treatment studies? This section will introduce the current challenges and future potentials.

The current HER2 status evaluation system was established to identify HER2-positive tumors instead of distinguishing HER2-low tumors from HER2-zero tumors.² Since the evaluation of the HER2 breast cancer subtype is based on IHC staining, the results might seem different to different inter-

preters. The IHC score is based on the visible result of the staining area, which can be inaccurate and doubted. In a recent study, 18 pathologists were asked to read and score 170 breast cancer biopsies. The result shows that the concordance rate of distinguishing IHC 0 from IHC 1+ was 26% among the 18 pathologists. In other words, the diagnosis of HER2-low (IHC 1+) or HER2-zero (IHC 0) can be different based on the pathologists' observations. This is an issue as new ADCs or other drugs are approved to be used in HER2-low tumor treatment. Patients who are inaccurately diagnosed might lose the opportunity to receive such therapies that might be helpful to them. Therefore, a new and improved version of the evaluation of HER2 status should be developed and replace the current one. One solution to this issue is the application of quantitative continuous scoring (QCS). QCS is a learning model that can help with detecting the expression of the HER2 protein by visualizing IHC staining results. Analysis shows that the correlation of QCS results and pathologists' results is high ($R=0.993$), proving that it can help overcome the conflict with the identification of HER2 expression status.¹⁶

Although antibody drug conjugates (ADCs) have become drugs that are phenomenal in anticancer research, resistance to them is a challenge to scientists. Since ADCs' mechanism has multiple steps, resistance to the drug can happen at any level.¹⁷ In antigen recognition and expression, the most concerning issue is the status of HER2 expression. Continuous exposure to ADCs can lower the amount of HER2 expression, making the tumor cells with lower HER2 proteins thrive without being killed by the potent drugs.¹⁸ Moreover, ADCs like trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd) are usually used in second-line treatment. Treatment from previous lines might have reduced the expression of HER2, for example, chemotherapy, trastuzumab, and pertuzumab. Resistance might occur if the ADC cannot detect and bind to the receptors. The bystander effect can overcome this issue.¹⁷ ADCs like trastuzumab deruxtecan have a better ability to cross the membrane and enter other tumor cells regardless of the amount of expression. Resistance can also occur after the ADC enters the tumor cells, known as intracellular resistance.

Currently, researchers are committed to finding new and more advanced drugs and treatments for metastatic HER2-associated breast cancer. ADCs like trastuzumab deruxtecan are waiting for approval and are expected to have great potential in increased efficacy and decreased risks, resistance, and side effects.

■ Conclusion

Breast cancer is one of the most common cancers in the world, especially among women. HER2, estrogens, and progesterone are three factors that can trigger abnormal cell growth. Tumors with overexpression of HER2 are HER2-positive, often treated with anti-HER2 drugs. HER2-low and HER2-zero subtypes were derived from the HER2-negative group, having low or no expression of HER2 protein. These tumors often receive endocrine therapies, depending on the expression of the hormones. However, trastuzumab deruxte-

can (T-DXd), an antibody drug conjugate that was previously used in second-line treatment for HER2-positive tumors, was proven to be helpful in HER2-low tumor treatment. The discovery of such drugs set up the future directions for research in breast cancer, but also created some issues that have yet to be resolved. To provide precise medication, the categorization of HER2 breast cancer subtypes using IHC score can be updated. This will allow clearer identification of HER2-low tumors from HER2-negative tumors, allowing more efficient treatments as new drugs like T-DXd are developed. Adaptation of more standardized systems can also improve the accuracy in identification by increasing the concordance of pathologists' observations and evaluations. In response to efficacy and resistance, more research diving into the mechanism of drugs and HER2 dimerization can suggest more helpful treatment combinations. Ultimately, by marrying objective, machine-learning diagnostics with highly tailored combination therapies, the medical community can move beyond general classification systems and transition into a highly individualized, highly adaptable era of cancer care.

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