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# Metastatic human epidermal growth factor receptor 2-positive breast cancer: Management, challenges, and future directions

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ABSTRACT

HER2 is over-expressed or amplified in 15–20% of breast cancer. Significant progress has been made in the treatment of metastatic HER2+ breast cancer. This is largely due to successful targeting of the HER2 pathway. There are several approved agents in the metastatic setting. However, treatment resistance frequently develops and tumors eventually progress. In recent years, our understanding of mechanisms of resistance has evolved. It is generally accepted now that HER2-positive breast cancer is not one disease. New therapeutic strategies and a tailored approach to management are necessary to maximize patient outcomes and minimize toxicity.



## Introduction

Approximately 15%-20% of breast cancers overexpress human epidermal growth factor receptor 2 (HER2). HER2-positive breast cancers are more aggressive, have a propensity for central nervous system (CNS) metastasis, and, historically, carry a poor prognosis. However, with further

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understanding of HER signaling and development of targeted HER2 therapies, patient outcomes have improved dramatically. Despite significant improvement in treatment outcomes, treatment resistance remains a major clinical problem in metastatic HER2 breast cancer. In recent years, there has been increased appreciation of the heterogeneity of HER2-positive breast cancer and the challenges in management it poses, highlighting the need for a more individualized approach.

## HER network

The human epidermal growth factor receptor (ErbB or HER) network is a family of 4 proteins with an extracellular ligand binding domain, a single transmembrane region, and cytoplasmic tyrosine kinase domain that result in potent cell signaling.[1] This network is robust owing to several internal connections, redundant pathways, and positive feedback loops which make it difficult to block completely.[2] It has been extensively studied because of its role in multiple cancers and potential for therapeutic targeting.

The receptors bind epidermal growth factor (EGF)-ligands, which results in a conformational change and allows for receptor heterodimerization or homodimerization and phosphorylation of cytoplasmic tyrosine kinase. HER1, also known as EGFR, and HER4 are automatous and bind a diverse group of ligands. HER1 and HER4 activation results in direct stimulation of multiple cell regulatory pathways including MAPK pathway and indirect activation of PI3/AKT pathway.[2] The HER2 receptor does not bind a ligand, but has a permanently open dimerization arm, thus making it the preferred partner to form dimers.[3] Receptor dimerization further strengthens the signaling layer by decreasing lysosomal targeting and increasing receptor recycling.[4] This gives HER2 a major regulatory role as an amplifier of the network through dimerization of the other receptors. Both HER2 and HER3 are nonautomatous. HER2 requires dimerization with a ligand-bound receptor to activate its receptor tyrosine kinase (RTK), whereas HER3 has a defective RTK that needs to bind both a ligand and dimerize with another HER receptor to be phosphorylated.[1] When bound to HER2, HER3 shows increased affinity for ligands and increased activity of RTK. More importantly, HER2-HER3 dimers are potent activators of PI3K-AKT pathway that promotes cell survival. HER2 receptor is an important regulator of the network as it acts through positive feedback loops to promote the HER receptor network as well as stimulate downstream MAPK and PI3/AKT pathways. Thus, dysregulation and overexpression of HER2 can promote oncogenesis.[2]

## Drugs targeting HER2

Table 1 summarizes the most widely studied drugs targeting HER2 and their mechanism of action. Trastuzumab is the hallmark drug in HER2-positive breast cancer. It is a designed

**Table 1**
Drugs for HER2-targeted therapy.[a]

| Drug | Class | Mechanism of action |
|---|---|---|
| Trastuzumab | Monoclonal antibody against HER2 (Domain IV) | Decreased receptor dimerization<br>Increased receptor endocytosis and destruction<br>Decreased receptor recycling<br>Stimulation of ADCC[a] |
| Pertuzumab | Monoclonal antibody against HER2 (Domain II) | Inhibition of receptor dimerization (particularly HER2-HER3) |
| T-DM1 (trastuzumab entamustine | Antibody drug conjugate | Retained functions of Trastuzumab<br>Inhibitory effect on microtubules |
| Lapatinib<br>Afatinib<br>Neratinib | Tyrosine kinase inhibitor | EGFR and HER2 selective receptor tyrosine kinase inhibitors |

[a] Antibody-directed cell-mediated cytotoxicity