

# Advances in therapy of breast cancer: overexpression and therapeutic implications of targeting human epidermal growth factor receptors

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**Received:** 11 March 2019

**Revised:** 26 March 2019

**Accepted:** 03 April 2019

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## ABSTRACT

The human epidermal growth factor receptor 2 (HER2) ERbb2 gene is amplified in approximately 25% of breast cancers. Characteristics of HER2-amplified tumors include increased proliferation rates and a propensity for distant metastasis. The discovery of overexpression of HER2 in a subset of breast cancers was an important milestone in our understanding of the biology of the disease. This paved the way for the discovery of trastuzumab, a humanized monoclonal antibody targeting HER2. Trastuzumab is the foundation of treatment of HER2-positive breast cancers, demonstrating dramatic responses in patients with metastatic disease. Recent advances in our understanding of the interaction between HER2 and other members of the epidermal growth factor receptor family have led to the identification of newer agents, resulting in the expansion of the clinical armamentarium of available agents for the treatment of HER2-positive tumors. The biology of the ERbb receptor family, the use of HER2-targeted agents in breast cancer, and the advances in anti-HER2 agents that are currently in clinical development are reviewed here.

**Keywords:** Breast cancer, Human epidermal growth factor receptor 2 (HER2), Lapatinib, Trastuzumab

## INTRODUCTION

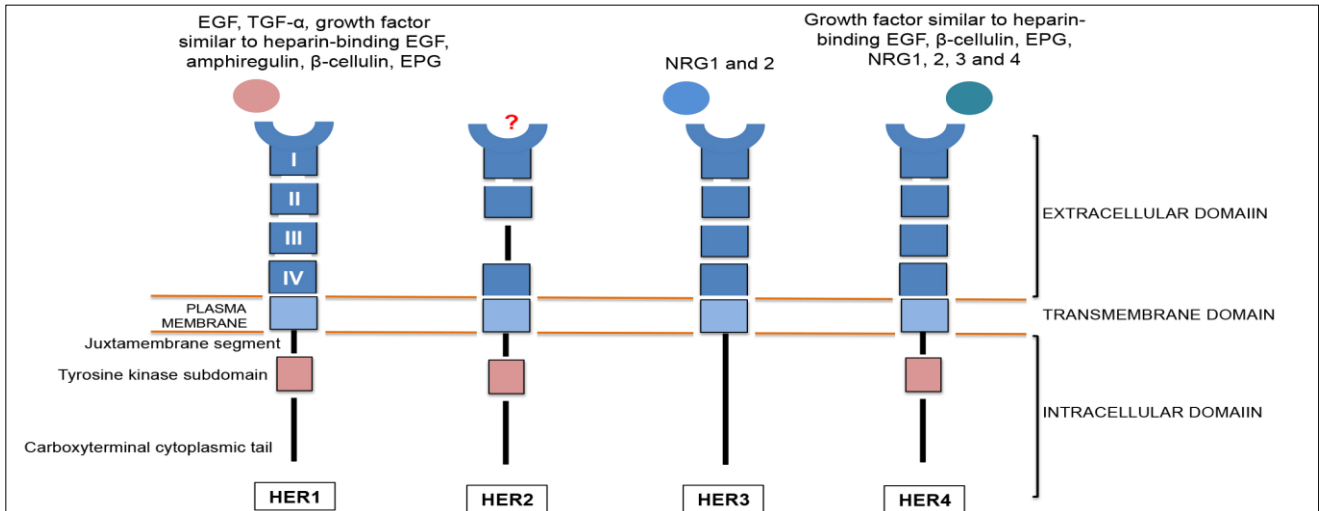
The human epidermal growth factor receptor 2 (HER2) ERbb2 gene is amplified in approximately 25% of breast cancers and encodes a transmembrane protein with tyrosine kinase activity.

HER2 belongs to the ERbb group of the protein kinase superfamily, which also includes epidermal growth factor receptor (EGFR [ERbb1]), HER3 (ERbb3), and HER4 (ERbb4). Although these receptors are important mediators of normal cell growth and development of various tissues, their activation has been associated with

the development and progression of several malignancies.<sup>1</sup> Members of the ERbb family of receptors contain 3 functional domains: an extracellular domain for ligand binding, a transmembrane domain, and an intracellular tyrosine kinase domain (Figure 1). Unlike other ERbb family members that require ligand binding for activation, signaling through the HER2 network occurs in the absence of a known ligand. The HER2 monomer exists in activated conformation and is the preferred dimerization partner for the other members of the ERbb family, especially HER3. Receptor dimerization is an essential first step to propagate an intracellular signal and occurs through homodimerization (between 2 HER2 molecules) or heterodimerization (between HER2 and other ERbb

receptors). Overexpression of HER2 results in augmented signaling through downstream phosphatidylinositol-3 kinase (PI3K) mitogen-activated protein kinase (MAPK) pathways. When the HER2 gene is amplified, dimerization

results in activation of a potent cell signaling cascade predominantly through the PI3K and MAPK pathways, leading to cell proliferation, angiogenesis, and tumor growth.<sup>2</sup>



**Figure 1: General arrangement of receptors HER1/2/3/4 and their natural soluble ligands.<sup>3</sup>**

Figure 1 shows that, the extracellular domain has four subdomains, and domains I and II are involved in binding the ligand. The carboxy-terminal tail contains tyrosine residues that can be phosphorylated. HER3 does not have a tyrosine kinase domain. To date, there are no known ligands for HER2. Epidermal growth factor (EGF), transforming growth factor alpha (TGF- $\alpha$ ), amphiregulin,  $\beta$ -cellulin, growth factor similar to heparin-binding EGF, epiregulin (EPG) and neuregulin (NRG) are the ligands referred to in Figure 1.

Figure 2 illustrates the therapies acting on HER/ErbB signalling. Trastuzumab is a humanized monoclonal antibody to subdomain IV of ErbB2. This leads to disruption of ErbB2-ErbB3 complexes, formed when ErbB2 is overexpressed. Pertuzumab is a humanized monoclonal antibody to subdomain II, the dimerization arm of ErbB2. Pertuzumab leads to inhibition of ligand-induced ErbB2 signaling, not of ligand-independent ErbB2 signaling. Lapatinib is a small molecule tyrosine kinase inhibitor of ErbB1 and ErbB2. Lapatinib blocks tyrosine kinase activity, independently of whether this activity has been triggered by a ligand or not.

### HER2 IN BREAST CANCER

HER2 is overexpressed in 15-30% of invasive breast cancers, which has both prognostic and predictive implications. Characteristics of HER2-amplified tumors include increased proliferation rates and a propensity for distant metastasis.<sup>4-6</sup>

### Trastuzumab

Trastuzumab is a monoclonal antibody that binds to domain IV of the extracellular segment of the HER2 receptor. Originally approved by the FDA in 1998 for metastatic disease, trastuzumab is the cornerstone of treatment for HER2-positive breast cancer and is a recombinant humanized monoclonal antibody that binds with high affinity to the extracellular juxtamembrane domain IV of HER2. Trastuzumab is the standard of care for both localized and metastatic disease, demonstrating improvements in disease-free survival and overall survival. Multiple mechanisms underlying the antitumor activity of trastuzumab have been proposed and include antibody-dependent cell-mediated cytotoxicity, inhibition of HER2 receptor dimerization, blockade of HER2 receptor extracellular domain cleavage, decrease in angiogenesis, inhibition of DNA repair, induction of cell-cycle arrest, and apoptosis.

Table 1 shows five pivotal trials involving more than 10,000 women which demonstrated that one year of trastuzumab therapy provided significant clinical benefit.<sup>7-9</sup> These trials demonstrated that inclusion of trastuzumab produces roughly a 50% improvement in disease-free survival and 33% improvement in overall survival, regardless of the chemotherapy regimen or sequence of trastuzumab delivery. In the metastatic HER2 breast cancer also, trastuzumab is recommended in the first-line setting. In a phase III trial, trastuzumab plus chemotherapy was associated with a significant improvement in time to

disease progression, objective response rate, and 1-year survival compared with chemotherapy alone.<sup>10</sup>

For patients with local–regional disease, the current standard of care is 1 year of adjuvant trastuzumab therapy. Trastuzumab may be administered after the completion of doxorubicin and cyclophosphamide in combination with paclitaxel or docetaxel, or may be concurrently administered with carboplatin and docetaxel. In the metastatic setting, Slamon et al, demonstrated in a pivotal phase 3 trial that trastuzumab in combination with chemotherapy significantly improved tumor response

(50% vs 32%;  $P < 0.001$ ) and median OS rate (25.1 vs 20.3 months;  $P = 0.046$ ) when compared with chemotherapy alone as first-line treatment.<sup>11</sup> Further studies highlighted the dependency of these tumors on the HER2 pathway, as administration of trastuzumab-based regimens after progression on trastuzumab continued to induce durable responses.<sup>12</sup> Extended obstruction of HER2 signaling with sequential trastuzumab-based therapy is critical to blocking the tumor's primary mechanism of growth and survival, and removing anti-HER2 therapy at progression results in an inferior patient outcome.<sup>12</sup>

**Table 1: Five pivotal trials for adjuvant trastuzumab in breast cancer.**

Study	Control arm	Trastuzumab arm	Reduction in relative risk of recurrence	DFS hazard ratio
NSABP B-31 (N = 2700)	AC → T	AC → TH	Joint analysis 52%	0.48
NCCTG N9831 (N = 3300)	AC → T	AC → TH		
HERA (N = 5090)	Any	Trastuzumab 1 year	46%	0.54
BCIRG 006 (N = 3150)	AC → D	AC → DH DCH	40% 33%	0.49 0.61
FINHer (N = 232)	D → FEC V → FEC	DH → FEC VH → FEC		0.42

NSABP, National Surgical Adjuvant Breast and Bowel Project; NCCTG, North Central Cancer Treatment Group; HERA, Herceptin Adjuvant Trial; BCIRG, Breast Cancer International Research Group; FINHer, Finland Herceptin Study. A, doxorubicin; C, cyclophosphamide; D, docetaxel; E, epirubicin; F, fluorouracil; H, trastuzumab; T, paclitaxel; V, vinorelbine; DFS, disease-free survival.

Trastuzumab is recommended at a dose of 4 mg/kg followed by 2 mg/kg weekly for breast cancer and 8 mg/kg followed by 6 mg/kg q3 weekly for gastric/gastroesophageal cancer. The duration of therapy is one year in adjuvant setting for breast cancer and till disease progression for metastatic breast, gastric, and gastroesophageal cancer. The most common adverse effects seen with trastuzumab are fever, vomiting, infusion reactions, diarrhea, headache, fatigue, rash, neutropenia, and anemia.

Overall, trastuzumab is well tolerated with minimal acute side effects. Although no significant differences in clinical efficacy between the anthracycline and nonanthracycline regimens can be discerned, the lower risk of cardiotoxicity and leukemia favors the use of a nonanthracycline-based regimen (docetaxel and carboplatin) with trastuzumab.<sup>13</sup> The reported incidence of cardiotoxicity ranges from 2% to 4% of exposed patients, particularly when used in conjunction with an anthracycline-containing regimen. Left ventricular dysfunction secondary to trastuzumab is thought to be mediated through inhibition of HER2 signaling and angiotensin 2-induced activation of reactive oxygen species in cardiac myocytes.<sup>14</sup> Recognized risk factors for trastuzumab-induced cardiotoxicity include

hypertension, age > 60 years, and an ejection fraction of < 55% at baseline.<sup>15</sup> In most cases, cardiac dysfunction related to trastuzumab is asymptomatic and decreases in ejection fraction are reversible. Left ventricular ejection fraction (LVEF) should be evaluated in all patients prior to and during treatment with trastuzumab.

Although trastuzumab remains one of the most effective therapies for metastatic HER2- amplified patients, a subset will present with primary refractory disease and most initial responders will develop progression. Several mechanisms for inherent or acquired resistance have been proposed, including inefficient trastuzumab binding, compensatory cross-talk with other ERbb receptors, as well as altered expression of downstream mediators of signaling pathways.<sup>16</sup> For example, proteolysis of the extracellular domain of HER2 by metalloproteases can lead to expression of the truncated and constitutively active form, p95HER2. This protein lacks the binding site for trastuzumab but retains the intracellular kinase activity. Other methods that decrease trastuzumab efficacy include interactions with other ERbb family members (eg, HER3) or their ligands and decreased levels of the tumor suppressor PTEN molecule.<sup>17</sup> A better understanding of these mechanisms has led to the development of next-

generation anti-HER2 agents that are specifically designed to ameliorate or bypass tumor resistance to trastuzumab.

The final analyses from the PHARE trial failed to show that 6 months of trastuzumab was noninferior to 12 months, suggesting that 12 months of adjuvant trastuzumab should remain the standard of care in patients with early HER2-positive breast cancer.<sup>18</sup>

### Lapatinib

Lapatinib is an orally active dual tyrosine kinase inhibitor which interrupts the HER2 and epidermal growth factor receptor (EGFR) pathways. Lapatinib is approved in combination therapy with capecitabine for HER2 overexpressing advanced and metastatic breast cancer patients who have received prior therapy including an anthracycline, a taxane, and trastuzumab. This was based on a study that demonstrated delay in time to disease progression when lapatinib was used in combination with capecitabine. The risk of disease progression was reduced by 51%, and the combination therapy was not associated with increases in toxic side effects.<sup>19</sup> Lapatinib is recommended at a dose of 1250 mg PO qDay on days 1–21 continuously in combination with capecitabine (2000mg/m<sup>2</sup>/day PO divided q12hr) on days 1–14 in a repeating 21-day cycle. Lapatinib is also approved in combination with letrozole for the treatment of postmenopausal women with hormone receptor and HER2 receptor positive metastatic breast cancers. The addition of

lapatinib to letrozole is well tolerated and leads to a significantly greater progression free survival, overall response rate, and clinical benefit rate than with letrozole alone.<sup>20</sup> The most common adverse effects with lapatinib are diarrhea, anemia, hand-foot syndrome, liver dysfunction, nausea, rash, and neutropenia.

### Pertuzumab

Pertuzumab is a humanized monoclonal antibody that blocks the activation of the HER2 receptor by hindering dimerization. Pertuzumab elicits action at a different ligand binding site from trastuzumab. It is approved in combination with trastuzumab and docetaxel in HER2-positive metastatic breast cancer patients previously not treated with hormone therapy or chemotherapy.

Emphasizing the impact of dual HER2 inhibition, pertuzumab combined with trastuzumab in the clinical setting results in dramatically superior outcomes when compared with trastuzumab-based regimens alone. When studied as first-line therapy in the phase 3 Study to Evaluate Pertuzumab + Trastuzumab + Docetaxel vs Placebo + Trastuzumab + Docetaxel in Previously Untreated HER2-Positive Metastatic Breast Cancer (CLEOPATRA), the addition of pertuzumab to trastuzumab and docetaxel significantly prolonged PFS (18.5 vs 12.4 months; HR, 0.62; 95% CI, 0.51–0.75; P < 0.001) compared with trastuzumab and docetaxel.<sup>21</sup> Results from this trial led to FDA approval of pertuzumab.

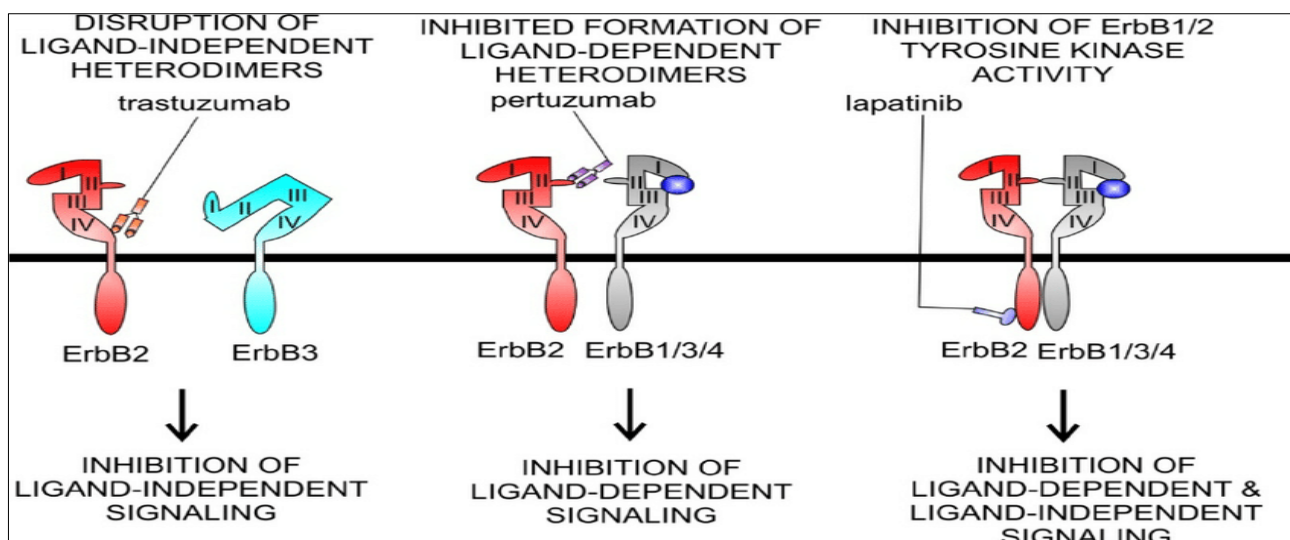


Figure 2: Mode action of current ErbB2 inhibitors.<sup>22</sup>

### Trastuzumab DM-1

Trastuzumab DM-1 (T-DM1), or trastuzumab emtansine or Ado-trastuzumab, is an antibody-drug conjugate (ADC)

consisting of the anti-body trastuzumab linked to the cytotoxic microtubule inhibitor DM-1. The ADC approach allows selective delivery of chemotherapy to tumor cells that express HER2 receptors, attenuating the adverse



effects associated with traditional chemotherapeutic agents. T-DM1 is often given as a single agent; however, the ADC mechanism likely makes this drug more similar to combination treatment than to monotherapy.

In the Open-Label Study of Trastuzumab Emtansine (T-DM1) vs Capecitabine + Lapatinib in Patients with HER2-Positive Locally Advanced or Meta-static Breast Cancer (EMILIA), T-DM1 was effective in the refractory HER2 population with minimal toxicity. Ado-trastuzumab is approved as a single agent for treatment of HER2-positive, metastatic breast cancer in patients who have already received trastuzumab and a taxane either separately or in combination. Approval was based on results from EMILIA trial, which showed a significantly prolonged progression-free survival and overall survival with less toxicity than lapatinib plus capecitabine.<sup>23</sup>

### Neratinib

Neratinib is an oral irreversible tyrosine kinase inhibitor of HER2 and EGFR. A phase II open label study in locally advanced breast cancer (LABC) showed a 16-week progression-free survival rate of 75% in trastuzumab-naive patients and 51% in previously treated disease.<sup>24</sup> Diarrhea was the most common grade 3/4 toxic effect (21%) in this study. Phase III evaluation of neratinib is ongoing in adjuvant trastuzumab-pretreated early-stage breast cancer. In the recent data from subgroup analyses from the phase III ExteNET trial has shown that Neratinib may have enhanced and sustained efficacy in patients with HR+ disease who initiate treatment within 1 yr of trastuzumab-based adjuvant therapy.<sup>25</sup>

### CONCLUSION

Therapies directed against HER2 have revolutionized the treatment of HER2 overexpressing breast cancer. Trastuzumab heralded a new era of targeted therapy as we continue to increase the number of agents available to patients with HER2-positive disease. Evolution of natural course of HER2-amplified breast cancer for the better is on evidence, and it is likely that these next-generation HER2-targeted therapies will have a similar impact on disease-free longevity. With the wealth of anti-HER2 agents available to treating physicians, secondary questions regarding the order and duration of therapy are raised.

*Funding: No funding sources*

*Conflict of interest: None declared*

*Ethical approval: Not required*

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**Cite this article as:** Bhalla A. Advances in therapy of breast cancer: overexpression and therapeutic implications of targeting human epidermal growth factor receptors. *Int J Basic Clin Pharmacol* 2019;8:1126-31.