

# Trastuzumab Resistance in HER2 Overexpressing Breast Cancer

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## Abstract:

HER2 is a tyrosine kinase that is overexpressed in around 20% to 25% of invasive breast tumours. Trastuzumab is a monoclonal antibody that has been humanised and is directed against HER2. Although most patients with metastatic breast cancer react initially to trastuzumab, disease progression occurs within one year of treatment. Numerous molecular mechanisms have been proposed to contribute to trastuzumab resistance development. They can be classified as impairing trastuzumab access to HER2, activating HER2 downstream signalling pathways, signalling via alternate routes, and impairing immune antitumor processes. However, because many of them exert similar effects, identifying the major signalling pathways involved in drug resistance would have a significant clinical impact. Significant effort is being made to identify other therapeutic modalities to complement trastuzumab treatment, either alone or combined with currently available modalities.

*Keywords* — **Breast cancer, HER2 signalling, trastuzumab**

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## I. INTRODUCTION

Breast cancer is the world's most prevalent type of cancer in women worldwide. Types of breast cancer includes invasive ductal carcinoma, when cancer cells grow into other parts of the breast tissue from the ducts, and could also metastasize to other parts of the body (1, 2). Monoclonal antibodies are found to be the most significant strategy in HERs-targeted therapies to block gene expression (3, 4). The monoclonal antibodies work by binding with Trastuzumab, located in the extracellular domain of the HER2 protein (5). This in turn would inhibit the rapid increase of HER2 overexpressing tumour cells (6). It could act as a single agent, where it will demonstrate an antitumor effect (6, 7). And when administered in a combination with a range of antineoplastic agents with additive and synergistic effects (8). This review aims to explore the signalling in which

breast cancer develop resistance to monoclonal antibody treatment.

## II. MULTI-TARGET OF HER2 AGENTS

HER2-targeted treatment can be used as single- (e.g. trastuzumab, pertuzumab and trastuzumab-MCC-DM1) or multi-targeted HER2 agents (e.g. pertuzumab, lapatinib) combined with standard systemic treatment (chemotherapy or hormone therapy, e.g. taxane, anthracyclines, anastrozole, letrozole) (9). Concerning the management of advanced HER2-positive BC, trastuzumab, pertuzumab, trastuzumab emtansine (formerly known as T-DM1) and lapatinib are approved as standard care for inhibiting HER2 activity in the treatment of HER2 positive MBC and for increasing the incidence of PFS, OS and overall response rate (ORr) when compared with chemotherapy alone or standard anti-HER2 molecule (10-13). Nevertheless, to date, only the

combining of trastuzumab and pertuzumab has an indication in the first-line setting (14).

### **III. Mechanisms of Trastuzumab Resistance**

One particular mechanism of trastuzumab resistance that has already been well documented in both preclinical models and clinical samples is considered noteworthy in this context (15, 16). In order to address this concern, one primary purpose is to determine which of all the mechanisms is clinically relevant. Clinical resistance, like that of other medicines, is expected to be complex (17, 18).

Human epidermal growth factor receptor 2 (HER2) has been truncated since distinct metalloproteases cleave the extracellular domain of the HER2, resulting in a truncated receptor unable to bind trastuzumab (19). Therefore, the membrane-bound portion, which still retains constitutively active kinase activity, retains HER2's binding affinity for trastuzumab but does not have the extracellular domain to bind it. The results from *in vitro* experiments indicated that trastuzumab could inhibit the cleavage of HER2, which led to a p95HER2 that remained in an active form (20). A retrospective clinical study discovered a strong correlation between the presence of p95HER2 and trastuzumab resistance in patients [50]. In metastatic breast cancer, the extracellular domain HER2 level has been investigated as a potential predictor of treatment response; however, the predictive values for clinical benefit with trastuzumab therapy were found to be low (21, 22).

MUC 4 and CD44/Hyaluronan Polymer Complex masking. The use of epitope masking has also been proposed as a resistance mechanism to trastuzumab in some patients. Mucin 4 (MUC4) is a glycoprotein-associated membrane consisting of multiple high glycosylated proteins, including mammalian epithelia, that are protective obstacles to epithelial cells. MUC4 can contribute to cancer progression in this way because it inhibits the immune system's detection of cancer cells, encouraging tumour proliferation, metastasis, and apoptosis suppression (23). MUC4 may obstruct the binding of trastuzumab by masking the HER2 receptor (23, 24). Expression of MUC4 was found to be associated with decreased antibody-binding

capacity in the human HER2-positive trastuzumab-resistant JIMT-1 cell line in a preclinical study, and it was discovered that using RNA interference to knockdown MUC4 could reverse resistance (25). CD44, a transmembrane hyaluronan receptor, mediates another HER2 masking mechanism that inhibits trastuzumab binding. Activation of CD44-mediated signalling pathways, including RAS and PI3K, has been demonstrated to occur upon binding of polymeric hyaluronan (4, 22). The binding of the hyaluronan polymer of the endogenously produced variety to CD44 enables PI3K/Akt activation [58]. By inhibiting CD44-hyaluronan polymer binding with anti-CD44 antibodies or hyaluronan oligomers, we could inhibit anchorage-independent tumour cell growth (26).

A mutation or transcriptional regulation has shown a loss in PTEN (phosphatase and tensin homolog) function in several tumours, almost 50 per cent of breast cancers included (27). PTEN does not inhibit PI3K activation; thus, PTEN deficiency results in constitutive PI3K/Akt activation (28). Lessened expression or activity of HER2 overexpression of breast cancer cells with PTEN blocked trastuzumab-mediated growth inhibition (28). There was study emphasised that the intra-carrying role of decreased PTEN protein expression leads to increased PI3K/Akt phosphorylation/signals, which prevents trastuzumab-mediated breast cancer cell growth arrest (29). Trastuzumab treatment was associated with significantly worse outcomes in patients with PTEN-deficient HER2-overexpressing metastatic breast cancer [33, 59] than patients with normal PTEN tumours (30).

Dependent on the cyclin-dependent kinase inhibitor p27KIP1 is another mechanism of trastuzumab resistance. Trastuzumab resistance is also encouraged when p27kip1 is suppressed (31). Inhibiting the cyclin-dependent kinase inhibitor p27 kip1 has growth inhibitory properties. A dramatic decrease in cell proliferation and enhanced apoptosis was observed in response to treatment with CDK2 inhibitors. Tumour growth was inhibited when CDK2 was inhibited *in vivo* (32). They believe that CDK2 inhibitors, which inhibit the CDK2 kinase, might be a viable option for

patients with breast tumours containing both HER2 and cyclin E co-amplification or overexpression (33). In the presence of trastuzumab, homodimers expressing cells might start MAPK and PI3K signalling even if they have been alone in culture for some time (34). Cumulative evidence supports the idea that HER3 is an essential participant in HER2-overexpressing breast cancer. EGFR/HER2 and HER2/HER3 receptor oligomerization properties verify that interactions with HER2/HER3 and HER2/HER3 receptors are detected with the ligand. Also, trastuzumab does not hinder HER2/HER3 dimerization.

The ligand of the HER family, called transforming growth factor  $\alpha$  (TGF  $\alpha$ ), is required for the formation of HER2 heterodimers. When tested in the lab, trastuzumab was less effective at inhibiting cell growth when applied in the presence of TGF- $\alpha$  (35, 36). Trastuzumab's growth-inhibitory properties were also blocked in HER2-overexpressing breast cancer cell lines by increased HER family ligands such as heregulin and EGF (37, 38).

The insulin-like growth factor-1 receptor (IGF-1R) is a transmembrane tumour necrosis factor (TK) receptor frequently expressed in human breast cancer. Its effectors promote proliferation and metastasis (39). HER-2 and IGF-1R both utilise the same post-receptor signalling pathways. IGF-1R, which interacts with HER2 in trastuzumab-resistant cell lines, also stimulates cell proliferation (39, 40). The first research article devoted to the molecular mechanisms underlying trastuzumab resistance identified IGF1R signalling as a contributory factor (41). Trastuzumab-mediated growth inhibition was lost in breast cancer cells overexpressing both HER2 and IGF1R, the authors demonstrated. Lack of sensitivity to trastuzumab and anti-IGF-1R drugs was linked to the presence of IGF-1R signalling in the cell prior to experimentation (42). Resistance to trastuzumab via IGF-1R appears to involve the PI3K/Akt pathway, resulting in increased degradation of p27 (43). Coefficient expression of HER2 and IGF-1R cancers may contribute to trastuzumab resistance (44, 45).

Angiogenesis is associated with increased expression of HER2 in breast tumours (46, 47). Trastuzumab treatment normalises and regresses the vasculature in a xenograft model of HER2-overexpressing breast cancer (48). This mechanism appears to be owing to the manipulation of several regulators of angiogenesis' complicated machinery (49, 50).

One possible mechanism of resistance is via the ER (ER stands for oestrogen receptor) (51). The oestrogen receptor's upregulation following treatment with lapatinib (anti-HER2 monoclonal antibody) suggests that the receptor may function as a redundant survival pathway (51, 52). Breast cancer growth appears to be characterised by crosstalk between the steroid hormone receptors for oestrogen (ER) and progesterone (PR) and the HER family. HER2, which results in cell proliferation even in the presence of trastuzumab, can also be transactivated by other hormones like prolactin acting by Janus kinase Activation (4, 53).

## CONCLUSIONS

HER2 overexpressing breast cancer is typically treated with trastuzumab, which is also effective in neoadjuvant, adjuvant, and metastatic settings. Nonetheless, there is significant concern about the presence of acquired and de novo resistance. The ability to recognise resistance mechanisms would allow new methods to keep resistance at bay or beat it. The introduction of novel targeted therapies has significantly altered approaches in metastatic settings. As of new standards of care, first-line treatment includes trastuzumab with pertuzumab and docetaxel, along with TDM-1 if trastuzumab-resistant. As is often the case with early-stage breast cancer, dual HER2 inhibition has been found to have promising results in the neoadjuvant setting. Several randomised trials are evaluating this strategy in the clinical settings. Although multiple targets are being investigated, predictive biomarkers are needed to help identify combination strategies that will benefit patients.

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