# Targeted Therapy for HER2-Positive Breast Cancer

Subjects: Oncology

Contributor: Angelica Ferrando-Díez, Eudald Felip, Anna Pous, Milana Bergamino Sirven, Mireia Margelí

The development of several antiHuman Epidermal Growth Factor Receptor 2 (HER2) treatments over the last few years has improved the landscape of HER2-positive breast cancer. Despite this, relapse is still the main issue in HER2-positive breast cancer. The reasons for therapeutic failure lie in the heterogeneity of the disease itself, as well as in the drug resistance mechanisms.

Keywords: breast cancer ; HER2-positive ; estrogen receptor positive ; triple-positive ; HER2-targeted therapy ; immunotherapy

## 1. HER2-Targeted Therapy

About 15–20% of breast carcinomas overexpress the Human epidermal growth factor receptor 2 (HER2) [1][2][3]. HER2-positive (HER2+) breast cancer (BC) is a heterogeneous and aggressive disease. Despite the dramatic improvement after the introduction of HER2-targeted therapy [4][5][6], 15–25% of patients in the early stage will still relapse [4][5][7][8]. Several neoadjuvant studies reported that response to anti-HER2 treatment might be determined by endocrine receptor status and intrinsic molecular subtypes [9]. However, they do not fully recapitulate tumor heterogeneity and other biological features have been linked to response heterogeneity to HER2-targeted therapy and the risk of relapse. In recent years, research has focused on developing novel drugs, including anti-HER2 therapies with alternative and optimized mechanisms of action and others targeting new potential pathways to prevent and overcome resistance.

In the neoadjuvant setting, dual HER2-blockade has significantly improved the pathologic complete response (pCR) rate, a potential surrogate endpoint of improved survival, with ranges of 40–65%, depending on the treatment regimens and duration of neoadjuvant treatment [1][8]. Beyond trastuzumab, other agents approved for early HER2+ BC include the monoclonal antibody pertuzumab, the antibody-drug conjugate (ADC) trastuzumab-emtansine (T-DM1) and the reversible HER2 inhibitor lapatinib. Dual HER2-blockade administered in combination with chemotherapy has improved the survival of patients with metastatic BC. Beyond these, new agents have also shown increased progression-free survival (PFS) and overall survival (OS) in the metastatic setting, such as trastuzumab-deruxtecan (T-DXd) or tucatinib in combination with capecitabine and trastuzumab [10][11].

Beyond the HER2 receptor, other therapies to overcome resistance are being actively investigated in HER2+ BC. One approach has been blocking the cyclin-dependent kinases 4/6 (CDK4/6) as they are downstream many of the cellular pathways associated with resistance to HER2-targeted therapies with a key role in cell cycle and proliferation. Different trials have explored these strategies with encouraging and promising results, but definitive results are needed [12][13].

In addition, HER2+ BC is known to be more immunogenic than other BC subgroups, with high variability between tumors; thus, different immunotherapeutic agents are under investigation in this setting, with controversial results obtained to date [14][15].

## 2. HER2-Positive Disease–Current Approaches

High expression of HER2 on cell surface of HER2 has been used as an ideal target by different mechanisms. Trastuzumab and pertuzumab are HER2-directed monoclonal antibodies (mAbs) inducing the recruitment of several immune cells with a subsequent activation of passive immunity, in combination with chemotherapy, these agents downregulate the oncogenic intracellular pathways led by HER2 activation via homo- and hetero-dimerization in the cancer cell membrane [16]. This happens because pertuzumab, by lying on the dimerization interface of HER2, prevents the formation of the potent heterodimer HER2/HER3. This combined approach has shown synergy due to the relevant interactions between them and the immune system, leading to antibody-dependent cellular toxicity [17].

In recent years, HER2-directed ADCs have been developed using HER2 receptor to deliver cancer-killing agents inside the tumour cells with high sensitivity. For example, T-DM1 or T-DXd produce an increased cytotoxic effect in target cells and reduce target side effects [6]. These agents are molecules formed by an antibody linked to a chemotherapeutic agent, showing high efficacy due to the inherent activity of both the antibody and the chemotherapeutic agent but also, and especially in the case of new ADCs such as T-DXd, because they have an immune-modulator effect that affects neighboring cells [18][19].

Other options for targeting HER2+ BC include lapatinib, neratinib or tucatinib, small-molecule tyrosine kinase inhibitors (TKI). Lapatinib is an oral reversible inhibitor of the epidermal growth factor receptor (EGFR) and HER2 blocking the phosphorylation of tyrosine kinase residues. Consequently, it inhibits cell proliferation by regulating the mitogen-activated protein kinase (MAPK) and PIK3 pathways [20]. Neratinib, another oral irreversible inhibitor of EGFR, HER2 and HER4 [21], has been proven to induce cell cycle arrest and decrease HER2+ cell proliferation in preclinical studies [21]. Tucatinib is a selective and reversible HER2 inhibitor that potently inhibits signal transduction downstream of HER2 and HER3 via the MAPK and PI3K/protein kinase B (AKT) pathways [22]. Some studies have reported that patients who progress after trastuzumab might benefit from a TKI with or without trastuzumab, which may aid to overcome resistance [11][23][24][25][26].

Finally, a bidirectional crosstalk between HER2 and other receptors involved in BC such as Notch or TGF-β signaling, lead to resistance to different anti-HER2 treatments and involve higher aggressivity of HER2+BC disease. Although there are not current strategies under development targeting those pathways, their assessment might be useful as predictive and prognostic biomarkers.

## 3. The Role of the Estrogen Receptor in HER2-Positive Tumors

Despite the obvious biological difference, HER2+/ER+ tumors are not yet treated differently from HER2+/ER- BC, and endocrine therapy is only added as maintenance after a standard anti-HER2 agent in combination with chemotherapy. However, in the last years, the effort has been focused on finding combinations to improve chemotherapy regimen toxicity. One example is the PHERgain phase II trial, in which 67% of the patients were ER+. A trastuzumab plus pertuzumab chemotherapy-free regimen was evaluated, and hormone therapy was added in ER+ patients. Although the chemotherapy-free regimen had a significantly lower pCR rate after the neoadjuvant regimen, 35.4% of the patients achieved a pCR after neoadjuvant treatment. Interestingly, with the addition of endocrine therapy, ER+ status was not a predictor of treatment response. However, the HER2 immunochemistry score had an impact on pCR: a HER2 3+ immunohistochemistry score achieved a higher pCR rate than tumors with a 2+ score [27]. Another example is the PERTAIN phase II trial, that combined an aromatase inhibitor (AI) (anastrozole or letrozole) plus trastuzumab, with or without pertuzumab in HER2+/ER+ metastatic BC patients with no prior systemic therapy. The AI plus trastuzumab and pertuzumab group had a significant increase in mPFS, 18.89 vs. 15.80 months (hazard ratio, 0.65; 95% CI, 0.48 to 0.89; $p$ = 0.007) [28]. Understanding the biological crosslink between the HER2 and ER pathways will help improve treatment and, therefore, patient outcomes in the future.

## 4. Role of Tumor Immunity in HER2-Positive Breast Cancer

The role of immunotherapeutic agents in HER2+ BC is becoming increasingly relevant as this BC subgroup has higher stromal TIL levels, implying that HER2+ disease is usually more immunogenic compared with other BC tumors [29][30][31]. Thus, several immunotherapeutic agents, such as novel HER2-directed mAbs, ADCs, vaccines and adoptive T cell therapies are currently being explored in patients with HER2+ tumors. However, not all HER2+ tumors are equally immunogenic and specific BC molecular subgroups beyond immunohistochemical (IHC) subtypes show differential responses. Interestingly, HER-2 subgroup is more immunogenic than Luminal A/B [32]. Both the percentage of TILs and the expression of different immune cells in the tumor microenvironment (CD8+, CD4+ Th1 and NK cells) have been associated with better prognosis; they may also contribute to the therapeutic effects of anti-HER2 targeted therapy [33].

In HER2+ BC, the interaction between the immune system and the tumor is complex and dynamic, involving different HER2-targeted treatments with chemotherapy and hormonotherapy, which modulate the action of HR status and tumor biology [30]. In addition, the different anti-HER2 treatments seem to modulate the tumor microenvironment and vice versa and the presence of high tumor immunity has been linked to a differential effect of these therapies [34][35]. For example, in vivo models, lapatinib stimulates tumor infiltration by CD4 + CD8 + IFN-γ-producing T cells via a STAT1-dependent pathway. The deficiency of STAT1 decreases the therapeutic efficacy of lapatinib, remarking the importance of immune activation in the lapatinib antitumor activity [36]. Another example, from the Neo ALTTO trial, is that T cell-driven immune signatures have been associated with pCR in patients treated with lapatinib, which highlights the role of immunity in modulating the activity of HER2-targeted therapy [36][37]. The expression of PD1 in the tumor microenvironment is a

mechanism of tumor evasion, the combination of anti-HER2 monoclonal antibodies with anti-PD1 is synergic, improving therapeutic activity, reason why these combinations are being tested in different trials [38].

Furthermore, the modulation of immune cells occurring in HER2+ BC has shown a clinical impact on treatment efficacy [39] [40]. In HER2+ BC, the NeoSphere [41] and NeoALTTO [42] trials have shown that tumors with low baseline TILs had lower pCRrates. Additionally, both NeoALTTO [42] and TRYPHAENA [43] trials found that TILs were associated with improved event-free survival when systemic therapy was given in the neoadjuvant setting. Loi et al., reported that TILs were predictive of benefit to adjuvant trastuzumab in the FinHER study [44]. A pooled analysis of six prospective neoadjuvant clinical trials found that increased TIL levels were associated with higher pCR rates and improved DFS in HER2+ BC [45]; however, the analysis did not show an association between increased TIL levels and OS. In contrast, in the adjuvant N9831 trial, patients who received chemotherapy alone, the presence of high TIL levels was significantly associated with an improvement in recurrence-free survival; on the other hand, this benefit was not seen in patients treated with chemotherapy plus trastuzumab [46]. In summary, higher levels of TILs have been correlated with better outcomes and response to anti-HER2 treatment; however, an enhanced understanding of the role played by the immune system in modulating therapy response to different anti-HER2 agents is still needed.

Due to the promising role of immunotherapy in HER2+ BC, the recent introduction of immune checkpoint inhibitors and other immunotherapeutic agents capable of unleashing an anti-tumoral immune response opens new possibilities for therapeutic combinations in this setting.

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