Human epidermal growth factor receptor 2 (HER2)-positive and hormone receptor-positive breast cancer: new insights into molecular interactions and clinical implications

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Recent data show a significant benefit from combining an anti-HER-2 agent with endocrine therapy in HER2-positive and hormone receptor (HR)-positive metastatic breast cancer. However, as the clinical outcomes achieved by these combinations do not favourably match those with chemotherapy, clinicians still perceive HER2-positive breast cancer as an homogeneous group and consider chemotherapy with anti-HER2 agents as the preferred treatment option, regardless of the HR status. Indeed, in HR-positive HER2-positive tumours, chemotherapy with anti-HER2 agents is the backbone of treatment, while endocrine therapy is commonly used in sequence when HR and HER2 are co-expressed rather than as a real alternative. Emerging biological and clinical data challenge this paradigm, suggesting that HER2-positive tumours are rather heterogeneous that HRs co-expression may account for part of this heterogeneity and, finally, that chemotherapy may represent an overtreatment in selected cases. The present review aims to summarise the biological features of HER2-positive breast cancer according to HR status, the role of the bi-directional cross-talk between HER2 and HR pathways on resistance development to anti-HER2 and endocrine therapy, and finally, the novel therapeutic strategies, including but not limited to chemotherapy, targeting these two pathways.

Key words: breast cancer, cancer metastasis, drug therapy, her2/neu, hormone receptors, resistance

introduction

Amplification and/or overexpression of the human epidermal growth factor 2 (HER2) oncogene, which belongs to the epidermal growth factor receptor (EGFR/HER) family, occurs in about 15% of invasive breast cancers, and enables constitutive activation of growth factor signalling and triggering breast cancer cell survival, proliferation, and invasion [1, 2]. Tumours with HER2 amplification and/or overexpression—herein after HER2-positive breast cancer—are characterised by poor clinical prognostic features, which translate into aggressive tumour behaviour [1] and, importantly, by experimental and clinical resistance to endocrine therapy. Current treatment of patients with HER2-positive disease is primarily represented by chemotherapy combined with HER2-targeted therapy, both in the adjuvant and in the metastatic setting [3–6]. This approach has dramatically changed the natural history of HER2-positive breast cancer and is often suggested as a first line option of choice for patients with metastatic disease [7].

Recent studies suggest that HER-2 positive breast cancer is biologically and clinically heterogeneous. Analysis on 169 HER2-positive early breast cancer by the 70-gene MammaPrint signature reported that the 22% of cases were classified as having good prognosis, with a 10-year distant disease-free survival (DFS) of 84%, even in the absence of (neo)adjuvant therapy with trastuzumab and chemotherapy. Of note, the distant DFS for HER2-positive breast cancer patients classified as having a poor prognosis signature was 55% [8]. Therefore, a minority of patients with HER2-positive breast cancer patients present an excellent prognosis even in the absence of treatment. Hormone receptor co-expression may partially account for such heterogeneity. For example recent data from neoadjuvant studies suggest that response to therapy with anti-HER2 agents largely depends on HR status [9, 10].

The present review explores the biological features and clinical behaviour of HER2-positive breast cancer according to HR status, describes the bi-directional cross-talk between HER2 and HR pathways and its implication on resistance development.
to anti-HER2 agents and endocrine therapy, and illustrates the novel therapeutic strategies, including but not limited to chemotherapy, employable in the HER2-positive and HR-positive breast cancer patients.

immunohistochemical and genetic subtyping of HER2-positive and HR-positive tumours

While about 10% of estrogen receptor (ER)-positive tumours reveal HER2 overexpression, among the subgroup revealing HER2 amplification and/or overexpression, about half are ER positive. ER-positive tumours overexpressing HER2 in general express ER at a lower level compared with ER-positive tumours of the luminal A class [11]. Of note, in HER2-positive tumours, ER and HER2 levels are inversely correlated at both the RNA and the protein levels [12, 13]. A number of published reports consistently indicate that HER2-positive breast cancers show different clinical characteristics and prognosis according to the IHC status of HRs [14–16]. For example HR co-expression seems to mitigate adverse prognosis in HER2-positive operable breast cancer patients. More recently, data with the PAM50 demonstrated that up to one-third of HER2-positive early breast cancer may be intrinsically classified as luminal A or B. Of note, the HER2-enriched subtype according to PAM 50 signature predominates in HER2-positive and ER-negative cases (35%–51%) and predicts response to neoadjuvant trastuzumab-based chemotherapy [17, 18].

An additional evidence that HER2-positive tumours heterogeneity is related to the HR co-expression came from a study integrating DNA copy number arrays, DNA methylation, exome sequencing, messenger RNA arrays, micro RNA sequencing and reverse-phase protein [19]. In particular, a HER2-enriched mRNA (HER2E-mRNA) subtype/HER2-positive group was characterised by increased expression of tyrosine kinase (TK) receptors FGFR4, EGF, HER2 itself together with genes within the HER2 amplicon (i.e. GRB7). A second group, called luminal-mRNA subtype/HER2-positive, enriched in HR-positive tumours, showed a higher expression of luminal genes like GATA3, BCL2 and ESR1. These two groups presented also distinct recurrent somatic mutations and protein expression patterns. Further studies are warranted to prospectively confirm these findings. Collection and analyses of tumour tissue are also needed to dissect the role of ER pathway in HER2 signalling and vice-versa and to identify novel predictive biomarkers and more targeted therapeutic strategies.

differential sensitivity of HER2-positive tumours to combinations of chemotherapy and HER2-targeting agents according to HR status

Since the pivotal trial published by Slamon et al., the therapeutic platform of chemotherapy combined with HER2-targeting has undergone a constant development through randomised trials in the metastatic setting. Table 1 summarises the details of most of the influential clinical studies in the first-line setting (details of each trial are reported in the supplementary Appendix, available at Annals of Oncology online). Chemotherapy and anti-HER2 agents combination is often considered a preferred first-line option for most patients with HER2-positive disease [7], regardless of HR status, based on the following evidence: (i) retrospective analyses of patients treated in the pre-trastuzumab era showed that, overall, HER2-positive tumours are more chemo-sensitive than their HER2-negative counterparts, especially when anthracycline-containing regimens are used; [20] (ii) as single agents, both trastuzumab and lapatinib are modestly active; [21–25] (iii) pre-clinical studies have suggested synergistic effects between trastuzumab and agents such as paclitaxel, docetaxel, vinorelbine and platinooids; [26] and (iv) the pivotal trial [3] and a myriad of phase II studies, including one influential randomised trial, [4] confirmed the cooperative effects of chemotherapy and trastuzumab, resulting in impressive gains in response rates (RRs), progression-free survival (PFS) and OS.

Newer regimens with double HER2 targeting, such as the one used in the experimental arm of the ‘Clinical Evaluation of Pertuzumab and Trastuzumab (CLEOPATRA) study’, have established a newer efficacy benchmark for future developments [27].

The ‘chemotherapy plus HER-targeting’ paradigm has been translated into the management of patients with operable breast cancer, where all randomised studies have been designed to include this monoclonal antibody in conjunction with chemotherapy, for treatment, again regardless of the HR status [6, 28, 29].

However, the biological heterogeneity of HER2-positive tumours according to HR status may have potential therapeutic implications. A correlation between hormone-receptor levels and endocrine responsiveness/reduced chemosensitivity is already recognised in HER2-negative tumours [30, 31], where increased ER and PR are associated with endocrine responsiveness and reduced chemosensitivity and, therefore, has therapeutic implications [32]. A recently published analysis in patients with HER2-positive metastatic tumours, treated with chemotherapy and trastuzumab showed that ER expression in more than 30% of cancer cells was associated with a significantly lower RR to treatment, compared with the RR observed in tumours with lower or absent ER expression [33]. However, regardless of RR, PFS of patients with ER-positive tumours was significantly improved when maintenance endocrine therapy was added to trastuzumab treatment. These results suggest that RRs with chemotherapy and trastuzumab may be lower than those summarised in Table 1 in HER2-positive tumours expressing high ER levels and that HER2-inhibition may overcome the de novo endocrine resistance of these tumours.

Data from recent neoadjuvant trials further support the hypothesis that, in HER2-positive tumours, the HR status influences response to anti-HER2-based therapy. Table 2 summarises the results of three of these trials where for the first time the pathological complete remission rate (pCR), a recognised surrogate of good clinical outcome [34], were reported according to hormone-receptor status. The ‘Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimization’ (NEO-ALLTO) and the ‘Neoadjuvant Study of
Pertuzumab and Herceptin in an Early Regimen Evaluation

(NEOSPHERE) trials were designed to deliver a short pre-
surgical treatment, followed by post-surgical adjuvant
chemotherapy and anti-HER2 therapy. In the ‘German
Preoperative Adriamycin and Docetaxel (GEPAR) QUINTO’
study, a full sequential anthracycline and taxane-based
chemotherapy regimen was delivered before surgery, and
trastuzumab was started concurrently with pre-operative
chemotherapy and continued after surgery to complete a year of
targeted therapy. Chemotherapy was part of the neoadjuvant
programme in all trials, with the exception of one arm of the
NEOSPHERE trial, where the association of trastuzumab and

**Table 1.** Phase III trials comparing chemotherapy ± HER2 targeting agents or different treatment combinations of chemotherapy and HER2 targeting agents

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Treatmenta</th>
<th>N</th>
<th>ORR (%)</th>
<th>PFS or TTP (months)</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>H0648g [3]</td>
<td>Randomised phase III, first-line MBC</td>
<td>Chemotherapy</td>
<td>234</td>
<td>32</td>
<td>4.6</td>
<td>20.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chemotherapy + Trastuzumab</td>
<td>235</td>
<td>50*</td>
<td>7.4*</td>
<td>25.1*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Docetaxel + Trastuzumab</td>
<td>92</td>
<td>61*</td>
<td>11.7*</td>
<td>31.2*</td>
</tr>
<tr>
<td>CHAT [80]</td>
<td>Randomised phase II, first-line MNC</td>
<td>Docetaxel + Trastuzumab</td>
<td>110</td>
<td>72.7</td>
<td>12.8</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Docetaxel + Trastuzumab + Capecitabine</td>
<td>112</td>
<td>70.5</td>
<td>17.9*</td>
<td></td>
</tr>
<tr>
<td>BCIRG 007 [81]</td>
<td>Randomised phase III, first-line MBC</td>
<td>Docetaxel + Trastuzumab</td>
<td>131</td>
<td>72</td>
<td>11.0</td>
<td>37.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Docetaxel + Trastuzumab + Carboplatin</td>
<td>132</td>
<td>72</td>
<td>10.4</td>
<td>37.4</td>
</tr>
<tr>
<td>US Oncology [82]</td>
<td>Randomised phase III, first-line MBC</td>
<td>Paclitaxel + Trastuzumab</td>
<td>98</td>
<td>36</td>
<td>7.1</td>
<td>32.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paclitaxel + Trastuzumab + Carboplatin</td>
<td>98</td>
<td>52</td>
<td>10.7*</td>
<td>35.7</td>
</tr>
<tr>
<td>HERNATA [83]</td>
<td>Randomised phase III, first-line LABC or MBC</td>
<td>Docetaxel + Trastuzumab</td>
<td>143</td>
<td>59.9</td>
<td>12.4</td>
<td>35.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Docetaxel + Vinorelbine</td>
<td>141</td>
<td>59.9</td>
<td>15.3</td>
<td>38.8</td>
</tr>
<tr>
<td>CLEOPATRA [27]</td>
<td>Randomised phase III, first line LABC or MBC</td>
<td>Docetaxel + Trastuzumab + Placebo</td>
<td>406</td>
<td>69.3</td>
<td>12.4</td>
<td>N.R**</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Docetaxel + Trastuzumab + Pertuzumab</td>
<td>402</td>
<td>80.2*</td>
<td>18.5*</td>
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<tr>
<td>EGF30001 [84]</td>
<td>Unplanned subgroup analysis of randomised phase III trial, first-line LABC or MBC</td>
<td>Paclitaxel + Placebo</td>
<td>37</td>
<td>37.8</td>
<td>6.3</td>
<td>20.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paclitaxel + Lapatinib</td>
<td>49</td>
<td>63.3</td>
<td>9.1*</td>
<td>26.2</td>
</tr>
<tr>
<td>EGF104535 [85]</td>
<td>Randomised phase III trial, first-line MBC</td>
<td>Paclitaxel + Placebo</td>
<td>222</td>
<td>50</td>
<td>6.5</td>
<td>20.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paclitaxel + Lapatinib</td>
<td>222</td>
<td>69*</td>
<td>9.7*</td>
<td>27.8</td>
</tr>
<tr>
<td>TDM4450g [86]</td>
<td>Randomised phase II trial, first-line MBC</td>
<td>Docetaxel + Trastuzumab</td>
<td>70</td>
<td>58</td>
<td>9.2</td>
<td>~30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TDM1</td>
<td>67</td>
<td>64.2</td>
<td>14.2*</td>
<td>N.R.**</td>
</tr>
</tbody>
</table>

*The difference was statistically significant at the P < 0.05 level.
**The hazard ratio for overall survival was 0.64 favouring the combined arm (P = 0.005).
*See supplementary Appendix, available at Annals of Oncology online for details of treatments and schedule used in these studies.
MBC, metastatic breast cancer; LABC, locally advanced breast cancer; ORR, overall response rate (complete + partial remission); CBR, clinical benefit rate (complete + partial remission and disease stabilisation lasting 6 months or longer); PFS, progression-free survival; TTP, time to progression; OS, overall survival; N.R., not reached; CHAT, Capecitabine, Herceptin And Taxotere; BCIRG, breast cancer international research group; HERNATA, HERceptin plus NAvelbine or TAxotere; CLEOPATRA, CLinical Evaluation Of Pertuzumab And TRAstuzumab.

**Table 2.** Rate of pathological complete response (pCR) and hormone receptor (HR) status in neo-adjuvant studies with anti-HER2 agents

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Regimena</th>
<th>anti-HER2 agenta</th>
<th>Overall pCR rate (%)</th>
<th>pCR rate according to HR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEPA RQUINTO [87]</td>
<td>620</td>
<td>EC-Docetaxel</td>
<td>Trastuzumab</td>
<td>30.3</td>
<td>25.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lapatinib</td>
<td>22.7</td>
<td>16.2</td>
</tr>
<tr>
<td>NEO-ALTTO [9]</td>
<td>455</td>
<td>Paclitaxel</td>
<td>Trastuzumab</td>
<td>29.5</td>
<td>22.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lapatinib</td>
<td>24.7</td>
<td>16.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Trastuzumab + Lapatinib</td>
<td>51.3</td>
<td>41.6</td>
</tr>
<tr>
<td>NEOSPHERE [10]</td>
<td>417</td>
<td>Docetaxel</td>
<td>Trastuzumab</td>
<td>29.0</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pertuzumab</td>
<td>24.0</td>
<td>17.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pertuzumab + Trastuzumab</td>
<td>45.8</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>None</td>
<td>16.8</td>
<td>5.9</td>
</tr>
</tbody>
</table>

*See supplementary Appendix, available at Annals of Oncology online for details of treatments and schedule used in these studies.
pCR, pathological complete remission according to the definition given by each author for the main analysis; HR, hormone receptor; GEPA R, German Preoperative Adriamycin and Docetaxel; NEO-ALTTO, Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimization; NEOSPHERE, Neoadjuvant Study of Pertuzumab and Herceptin in an Early Regimen Evaluation.
pertuzumab was delivered pre-operatively without chemotherapy. The NEO-ALTTO and the NEOSPHERE trials included arms with combinations of HER2-targeting agents, whereas the GP-ENDOMETRO trial compared lapatinib with trastuzumab. Despite differences in the definition of the primary end point, the neoadjuvant studies with trastuzumab ± lapatinib and trastuzumab ± pertuzumab reported pCR rates ranging from 22.7% to 30% when a single HER2-targeting agent was given in addition to chemotherapy. The pCR rates increased to between 45.8% and 51.3%, respectively, when pertuzumab and lapatinib were added to trastuzumab and chemotherapy. The NEOSPHERE study reported a pCR rate of 16.8% in the arm with trastuzumab and pertuzumab without chemotherapy. This finding is remarkable as it suggests that a subgroup exists for whom anti-HER2 therapy alone may offer significant efficacy without the addition of chemotherapy.

Importantly, all the studies consistently showed that pCR rates to neoadjuvant therapy were significantly lower in ER-positive compared with ER-negative tumours (Table 2). This also occurred in the chemotherapy-free arm of the NEOSPHERE trial, where treatment led to disease eradication in about one-third of ER-negative tumours, compared with just 6% in their ER-positive counterparts. A similar observation was made in a small study exploring the activity of exclusive dual blockade therapy with lapatinib and trastuzumab in the neoadjuvant setting [35]. This ‘Translational Breast Cancer Research Council (TBCRC) 006’ trial reported an overall pCR rate of 42% after 12 weeks of therapy in HER2-positive/ER-negative operable and/or locally advanced breast cancer. Interestingly, in patients with HER2-positive/ER-positive disease, letrozole was added to lapatinib and trastuzumab, resulting in a pCR rate of 21%. This pCR rate favourably compares with that observed in the subset of HER2-positive/ER-positive tumours treated in the trastuzumab/pertuzumab arm of the NEOSPHERE trial. While this may result as being just an additive effect, the hypothesis that endocrine therapy may partially restore sensitivity to HER2-targeting is intriguing and deserves further study.

Lack of long-term survival data suggests that results of neoadjuvant trials should not impact on the way that early, HER2-positive breast cancer is currently treated. However, the rate of tumour response from neoadjuvant studies foster the use of HER2-targeted therapy in combination with endocrine therapy for advanced breast cancer patients with tumours that co-express high-levels of HRs.

differential sensitivity of HR-positive tumours to endocrine-therapy according to HER2 status

In ER-positive early breast cancer, endocrine treatment reduces the recurrence and mortality rates, regardless of the use of chemotherapy [36]. Clinical data suggest that overexpression of HER2 and the lesser-studied EGFR is associated with a poorer outcome in breast cancer patients treated with endocrine therapy [37–42]. However, data are not definitive as while some studies indicated no benefit or even a potentially detrimental effect of tamoxifen on outcomes in women with HER2-positive/HR positive tumours, [39, 40], other studies failed to show such effect [41, 42].

Neoadjuvant trials provide a unique platform to correlate molecular determinants of response and resistance with the clinical response of primary breast cancer to medical therapy. Results in this setting show more consistently that HER2 and, to a lesser extent, EGFR may act as mediators of resistance to tamoxifen. In women with locally advanced, HR-positive breast cancer randomised to neoadjuvant treatment with tamoxifen or with the aromatase inhibitor (AI) letrozole [43], letrozole significantly increased RR compared with tamoxifen. However, differences in RRs between the two drugs were most marked for ER-positive and EGFR and/or HER2-positive tumours, suggesting that the growth-promoting effects of these growth factor receptors on ER-positive breast cancer can be most effectively inhibited by potent estrogen deprivation therapy.

Dowsett et al. analysed changes in tumour proliferation occurring in patients randomised to another AI, anastrozole, tamoxifen or the combination of the two agents given for 3 months before surgery [44]. Similarly to the previously described trial, the superiority of anastrozole over tamoxifen in terms of RR was mostly observed in HER2-positive/HR-positive tumours. Intriguingly, after 2 weeks of treatment, tamoxifen was less effective than anastrozole in suppressing proliferation in HER2-positive tumours compared with HER2-negative tumours. Among patients receiving anastrozole at the end of 12 weeks of treatment, those with HER2-positive tumours showed a significantly lower degree of proliferation suppression than their HER2-negative counterparts as, after an initial response, resistance to AIs depending on HER2 signalling may rapidly emerge. A recent follow-up of the study by Ellis et al. also supports the idea that in HER2-positive/HR-positive tumours, there is an estrogen-independent signalling mechanism that leads to increased proliferation [45].

A retrospective analyses of the ‘Arimidex, Tamoxifen, Alone or in Combination (ATAC)’ and the ‘Breast International Group (BIG) 1’ studies, two large randomised trials of adjuvant endocrine therapy [46, 47], failed to demonstrate any interaction between type of endocrine therapy and HER2 status on long-term efficacy outcomes. Indeed, AIs were found to be more effective than tamoxifen in the overall patient population, regardless of the HER2 status. Importantly, HER2-positivity predicted a worse clinical outcome regardless of treatment type, confirming its role as a marker of resistance to endocrine manipulation in general.

HR and HER bi-directional cross-talk: implications on the development of resistance to endocrine therapy and anti-HER agents

Based on the above, clinically defined HER2-positive subtype of breast cancer is not clinically and biologically homogenous. There is increasing evidence that the ER and HER2 pathways cross-talk and thereby synergise in tumour progression. The following paragraphs summarise molecular evidence of such bi-directional cross-talk and its role in differential sensitivity to therapies.
HER/ER cross-talk as a mechanism for resistance to endocrine therapy

Aberrant signalling through the growth factor receptors pathway has long been identified as a mediator of resistance to endocrine manipulation in HR-positive cancer cells [48]. Clinical and laboratory evidence support a critical role for the cross-talk between the ER and HER2 signalling pathways in resistance to endocrine therapy [20], especially when both the receptors are co-expressed. Mechanisms of ER signalling in breast cancer are described in Figure 1. Estrogens, by activation of the ER nuclear function, can increase transcription and expression of ligands such as transforming growth factor-α (TGFα) and insulin-like growth factor 1 (IGF1) [49–51], that, in turn, can trigger the growth factor receptor pathway [50, 52].

Activation of the PI3K/AKT and the p42/44 MAPK pathways...
by these receptors, may subsequently result in phosphorylation of ER and its co-activator such as AIB1, thus leading to enhancement of genomic ER activities, even in the absence of its ligand, or in the presence of selective ER modulators (SERMs) such as tamoxifen [52, 53]. Phosphorylation of co-repressors, on the other hand, can result in their export from the nucleus, thereby preventing regulation of ER transcriptional complexes in the nucleus [54, 55]. Down-regulation of ER and PgR expression has been demonstrated to occur as a result of HER-mediated activation of the PI3K/akt and the p42/44 MAPK pathways [56, 57]. Thus, while receptor tyrosine kinases can activate the transcriptional function of the ER, they can also reduce estrogen dependence by down-regulating the expression of the ER or estrogen-related genes, such as the PgR. This could possibly contribute to the relative resistance to endocrine therapies in tumours harbouring abnormalities in HER receptors members.

Hurtado et al. [34] have recently shown that estrogen-ER and tamoxifen-ER complexes directly repress HER2 transcription. The Paired Box 2 transcription factor (PAX2) seems to be the mediator of this cross-talk and its loss or deregulation causes tamoxifen resistance by the acquisition of a HER2-driven phenotype in the ER-positive luminal cells.

In addition to genomic signalling [58], in breast cancer culture models, the membrane (nonnuclear) ER, bound to either oestadiol or tamoxifen [52, 55], by triggering EGFR, HER2, and IGFR1 [59] and their downstream pathways [60], ultimately contribute to tamoxifen resistance development by increasing nuclear ER gene transcription [61]. However, the average incidence of cytoplasmic ER in nearly 3200 cases of breast cancer was only 1.5%, strongly suggesting that its measurement is unlikely to be of routine clinical value at the present [62].

The following laboratory evidences suggest that inhibition of HER pathways may delay endocrine resistance onset and that the dual inhibition of both HER2 and ER pathways may exert optimal antitumour activity in HR and HER2-positive breast cancer.

In a xenograft model using MCF7 human breast cancer cells stably transfected with HER2 (MCF7/HER2-18) [63], the selective HER1 tyrosine kinase inhibitor gefitinib transiently slowed tumour growth. However, further studies have shown that complete inhibition of the HER pathway and its multiple potential homo- and heterodimer partners by combining several anti-HER inhibitors, such as pertuzumab (a HER2-specific monoclonal antibody that inhibits heterodimerization with other HER members), trastuzumab and gefitinib, or trastuzumab and lapatinib (a dual EGFR and HER2 TK inhibitor) is needed to achieve the best activity in HER2-positive/ER-positive breast tumour cells [64, 65]. Importantly, these potent anti-HER combinations were only modestly effective when implemented in the absence of concomitant endocrine therapy as, in such tumours, both ER and HER2 appear to drive tumour cell survival, and both pathways should be blocked for optimal outcome. These molecular findings have provided the rationale for clinical studies of endocrine therapy and HER2-targeting agents in an attempt to block growth factor signalling pathways and restore endocrine responsiveness [64, 66, 67].

**HER2/ER cross-talk as a mechanism for resistance to HER2-targeted agents**

Resistance to HER2-targeting has been intensively investigated in the last decade [68]. Until recently, there has been little recognition of the fact that up-regulation of ER expression and/or activity can function as an escape mechanism leading to resistance to HER2-targeted therapy in HER2 and HR-positive breast cancer patients. Preclinical studies show that in ER and HER2-positive breast cancer cell lines initially sensitive to lapatinib, enhanced ER signalling is evident upon acquisition of resistance to lapatinib and that this resistance may be prevented by the simultaneous inhibition of HER2 and ER signalling [69, 70]. Intriguingly, increased ER activity was also confirmed in patients with HER2 and ER-positive metastatic breast cancers progressing to lapatinib monotherapy [70]. An analogous phenomenon was also documented in chronically trastuzumab exposed patients, whose tumours revealed up-regulation of the ER [71].

To further elucidate the potential role of the ER in the onset of resistance to anti-HER2-targeted therapies, Wang et al. studied different HER2-positive human breast cancer cell lines with *de novo* or acquired resistance to trastuzumab, lapatinib, or lapatinib plus trastuzumab [72]. Authors found that with sustained HER2 inhibition, the ER functions as a key escape/survival pathway in HER2-positive/ER-positive cells and that a dynamic transition between HER2 and ER activity plays a role in resistance to lapatinib-containing regimens. Thus, in HER2-positive/ER-positive breast cancer cells, either the ER or HER2 can initially function as the major promoter of proliferation and survival. Eventually, however, with sustained, effective HER2 inhibition using lapatinib or lapatinib + trastuzumab, the ER becomes the primary controller of cell survival, resulting in resistance to lapatinib, or lapatinib + trastuzumab therapy. Findings from these studies underline the importance of dual inhibition of both HER2 and ER to achieve the best antitumour activity in ER-positive HER2-positive breast cancer and, if further confirmed in the clinical setting, will provide a strong rationale to optimise biologically targeted therapies, in selected breast cancer patients, by completely blocking the HER network, in conjunction with ER inhibition.

**novel strategies to optimise treatment in HER2-positive/HR-positive breast tumours**

A logical therapeutic approach in these HER2 positive and HR-positive breast cancer is to combine target therapies to block both ER and HER2 pathways. This hypothesis was explored in three trials conducted in patients with locally advanced and/or metastatic breast cancer (Table 3) [73–76]. While the ‘Trastuzumab and Anastrozole Directed Against ER-Positive HER2-Positive Mammary Carcinoma’ (TanDEM) and the ‘Efficacy and Safety of Letrozole Combined With Trastuzumab in Patients With Metastatic Breast Cancer’ (eLeCTRA) studies were phase III randomised trials conducted in HER2-positive/ER-positive breast cancer patients, the ‘EGF30008’ study was conducted in 1286 women with HR-positive breast cancer...
and endocrine agent either concomitantly with chemotherapy or receiving trastuzumab [78]. Interestingly, though, about a half of patients treatment, with only about 10% receiving endocrine therapy and 70% of these patients receive chemotherapy as part of a recent survey conducted in the United States shows that about HER2-positive, metastatic breast cancer patients [7]. In fact, a in favour of the use of chemotherapy-based combinations in the trials summarised in Tables 1 and 2, is a recurring argument [77]. However, the comparison of RRs and PFS results between patients with HER2-positive/HR-positive metastatic tumours [79]. Patients whose tumours show

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Treatment*</th>
<th>N</th>
<th>ORR (%)</th>
<th>CBR (%)</th>
<th>PFS (months)</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>TANDEM [73]</td>
<td>Randomised phase III trial, first-line MBC</td>
<td>Anastrozole</td>
<td>104</td>
<td>6.8</td>
<td>27.9</td>
<td>2.4</td>
<td>23.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anastrozole + Trastuzumab</td>
<td>103</td>
<td>20.3*</td>
<td>42.7*</td>
<td>4.8*</td>
<td>28.5</td>
</tr>
<tr>
<td>EGF30008 [75]</td>
<td>Pre-planned subgroup analysis of a larger randomised phase III trial, first-line LABC or MBC</td>
<td>Letrozole + Placebo</td>
<td>108</td>
<td>15</td>
<td>29</td>
<td>3</td>
<td>32.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Letrozole + Lapatinib</td>
<td>111</td>
<td>28*</td>
<td>48*</td>
<td>8.2*</td>
<td>33.3</td>
</tr>
<tr>
<td>eLEcTRA [76]</td>
<td>Randomised phase III, closed prematurely because of slow accrual, first-line MBC</td>
<td>Letrozole</td>
<td>31</td>
<td>13</td>
<td>39</td>
<td>3.3</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Letrozole + Trastuzumab</td>
<td>26</td>
<td>27</td>
<td>65</td>
<td>14.1</td>
<td>NR</td>
</tr>
</tbody>
</table>

*The difference was statistically significant at the P < 0.05 level.

Table 3. Summary of randomised trials evaluating the addition of HER2 targeting agents to first-line endocrine therapy with aromatase inhibitors in HER2-positive and hormone receptor-positive breast cancer patients

patients not selected on the basis of their HER2 status [74]. Almost 17% of the patients had centrally confirmed HER2-positive disease and were analysed separately as planned [75]. The three trials provided consistent results, indicating that the combination of an anti-HER2 agent and an AI significantly improved RR, clinical benefit rate (CBR) and PFS, compared with endocrine therapy alone. No significant difference on OS estimates was observed in any of the trials, possibly due to the influence of crossover, the lines of treatment after progression and to the number of events at the time of the analysis for the primary end point PFS, when 47% and 58% of death had occurred in the EGF30008 and TANDEM, respectively. These trials provided a strong proof-of-concept for these chemotherapy-free therapeutic options. However, the complexity and redundancy of the HER network may require more complete inhibition of the HER family receptors by combining different anti HER2 agents with endocrine therapy to further optimise clinical efficacy, an option currently tested in ongoing clinical trials.

The combination of endocrine therapy and trastuzumab or lapatinib is today an available first-line therapeutic option in patients with HER2-positive/HR-positive metastatic tumours [77]. However, the comparison of RRs and PFS results between the trials summarised in Tables 1 and 2, is a recurring argument in favour of the use of chemotherapy-based combinations in HER2-positive, metastatic breast cancer patients [7]. In fact, a recent survey conducted in the United States shows that about 70% of these patients receive chemotherapy as part of first line treatment, with only about 10% receiving endocrine therapy and trastuzumab [78]. Interestingly, though, about a half of patients receiving first-line chemotherapy and trastuzumab also received and endocrine agent either concomitantly with chemotherapy or added sequentially as a form of maintenance therapy.

**conclusions**

In the clinical practice, there is increasing recognition that HER2-positive breast cancer patients are not a homogeneous group. In particular, the HR status is emerging as a relevant stratification factor with practical clinical implications. Data from neoadjuvant studies show that HR status account for different sensitivity to treatments. Molecular analysis provides potential explanations for this effect, indicating that the HER and ER pathways are strictly related in a bi-directional way. HER2 signalling causes endocrine resistance and ER modulate the response not only to chemotherapy, but also to HER2 targeted agents. Finally, clinical trials have confirmed the preclinical rationale of combining endocrine therapy and anti HER2-agents to interfere with this cross-talk.

Two important points to discuss are (i) where combinations of endocrine agents and HER2-targeting agents can be currently considered a reasonable first-line option for HER2-positive/hormone-receptor positive metastatic breast cancer patients; (ii) what are the possible future developments of this therapeutic approach. Given that response rates to chemotherapy plus HER2-targeted therapy combinations typically exceed the 28% reported for these combinations, such an approach cannot be recommended in young patients or those with life-threatening or symptomatic disease. However, understanding that no treatment is curative in this setting, a therapeutic trial of this generally well-tolerated strategy, could be considered in postmenopausal patients with less extensive or asymptomatic metastatic disease. Such an approach offers the possibility of delaying initiation of a more toxic chemotherapy-based HER2-targeted combination for 6–12 months, and occasionally longer. In addition, despite lack of data from randomised trials, it seems reasonable to offer patients maintenance endocrine therapy with ongoing HER2 targeting once chemotherapy becomes too toxic or its benefits hit a plateau. The survey of patterns of care published by Tripathy et al. [78] shows that these concepts are being taken on by oncologists in the clinical practice.

We believe, however, that a real step forward would be represented by the identification of factors other than clinical features (i.e. age, performance status, pattern of disease) that may define patients where endocrine therapy combined with HER2-targeting agents may be an elective rather than a reasonable, option. For example high-hormone receptor expression [33] or belonging to a luminal, rather than ‘pure’HER2 intrinsic subtype may represent biomarkers of reduced efficacy of chemotherapy [79].
these features are, in our opinion, the optimal candidates for clinical trials assessing chemotherapy-free combinations. Despite the tremendous challenges in the research of biomarkers that could predict treatment efficacy, large tissue-banks have been collected in the context of neoadjuvant randomised trials. Hopefully, these efforts will provide candidate biomarkers that may further define personalised treatment strategies patients with HER2-positive breast cancer.

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references


A meta-analysis on dose–response relationship between night shift work and the risk of breast cancer

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This study aimed to conduct a systematic review to sum up evidence of the associations between different aspects of night shift work and female breast cancer using a dose–response meta-analysis approach. We systematically searched all cohort and case–control studies published in English on MEDLINE, Embase, PSYCInfo, APC Journal Club and Global Health, from January 1971 to May 2013. We extracted effect measures (relative risk, RR; odd ratio, OR; or hazard ratio, HR) from individual studies to generate pooled results using meta-analysis approaches. A log-linear dose–response regression model was used to evaluate the relationship between various indicators of exposure to night shift work and breast cancer risk. Downs and Black scale was applied to assess the methodological quality of included studies.

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