Combining trastuzumab (Herceptin®) with hormonal therapy in breast cancer: what can be expected and why?

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Received 28 January 2003; revised 31 March 2003; accepted 3 June 2003

Hormonal therapy and the humanised anti-HER2 monoclonal antibody trastuzumab (Herceptin®) represent one of the oldest and one of the newest treatment modalities for breast cancer, respectively. Recent data have suggested that HER2 overexpression is associated with resistance to hormonal therapy and there is considerable preclinical evidence to support the existence of interaction or ‘cross talk’ between HER2 and estrogen-receptor (ER) signalling pathways in breast cancer. Preclinical data also demonstrate that adding trastuzumab to hormonal therapy results in greater antitumour activity than either agent alone. The existence of an inverse relationship between ER expression and HER2 overexpression has also been well established clinically. Thus, a range of clinical trials are now ongoing to determine whether the addition of trastuzumab to hormonal therapy will provide breast cancer patients with benefits in clinical practice. This review describes the rationale for these trials and discusses the potential of therapeutic regimens combining trastuzumab with hormonal therapy.

Key words: anastrozole, breast cancer, estrogen receptor, HER2, letrozole, tamoxifen, trastuzumab

Introduction

Hormonal therapy has an important role in the management of estrogen receptor (ER)-positive breast cancer [1]. Women with primary, stage I/II breast cancer often receive adjuvant hormonal therapy to reduce the risk of disease recurrence following initial management using surgery and/or radiation. Hormonal therapy is also used in patients whose disease has metastatised, who may obtain clinical benefit (response or stable disease) for >6 months with one or more consecutive treatments.

The role of estrogen in breast cancer was suggested by work reported in 1896 [2], although the existence of estrogen was not known until the 1920s [3] and its mechanism of action in cancer was not described until the ER was identified in the 1960s [4]. Expression of ERs and/or progesterone receptors (PgRs) by breast tumours is now the best recognised molecular predictive marker for breast cancer, identifying those patients most likely to respond to hormonal manipulation. Treatment with the objective of modulating ER activity was probably the first therapy that could be termed targeted, in that the treatment modality is aimed at inhibiting a factor specifically involved in breast cancer behaviour. The subsequent introduction of the selective estrogen receptor modulator (SERM) tamoxifen and the aromatase inhibitors has been important in the refinement and increased use of hormonal therapy for breast cancer [5].

The concept of therapeutic targeting in breast cancer at a molecular level has been the subject of extensive research, leading to the development of a specific therapy for a subset of breast cancers. Human epidermal growth factor receptor-2 (HER2, neu or c-erbB-2) is a member of a family of transmembrane tyrosine kinases and HER2 amplification/overexpression has a pivotal role in breast development and growth [6–8]. As with hormonal therapy, recognition of the part that HER2 amplification/overexpression plays in breast cancer has led to the development of therapy specifically directed against the HER2 receptor [9]. The humanised monoclonal antibody trastuzumab has been demonstrated to have significant clinical activity in women with HER2-positive metastatic breast cancer, including a survival benefit when added to chemotherapy [10, 11].

It has recently been reported that HER2 overexpression is associated with preclinical and clinical resistance to hormonal therapy, particularly tamoxifen [12–14]. Thus, it has been suggested that combining hormonal agents with trastuzumab may represent a rational approach for study in future clinical trials in view of the targeted nature of these agents and their efficacy and tolerability profiles. This review discusses the evidence for inter-relationships between ER and HER2 pathways on the cellular level that may support the use of such a combination. The interactions described also apply to the HER2 and PR pathways.

Rationale for and classes of hormonal therapy

Estrogen and hormonal treatments for breast cancer mediate effects through the ER, which functions as a transcriptional factor controlling estrogen-related genes [15]. When a ligand such as oestradiol binds to the ER, the receptor becomes more capable of dimerisation due to activation of structural domains. The nuclear localisation of the ER–oestradiol dimers results in interaction with a variety of co-activator proteins, binding to estrogen response
elements and subsequent cell division [1]. The net effects of estrogen on ER-positive breast duct epithelium include increased cell proliferation and survival [15]. As such, it is a clinically useful predictive marker and treatment target.

The various classes of hormonal therapy utilised in the treatment of ER-positive breast cancer are designed to disrupt the stimulation of breast cancer cell proliferation by ER-mediated signalling (Figure 1). These include the so-called anti-estrogens, which can be broadly classified as non-steroidal SERMs such as tamoxifen, raloxifene and toremifene, ‘pure’ steroidal anti-estrogens such as fulvestrant, and the aromatase inhibitors, which include anastrozole, letrozole and exemestane [1, 16].

SERMs, such as tamoxifen, are competitive inhibitors of oestradiol binding to the ER and produce receptor complexes with limited activity [17]. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) has concluded that tamoxifen provides clear benefit for both premenopausal and postmenopausal women with ER-positive breast cancer and for those whose ER status is unknown [18]. In 1998, tamoxifen was also approved for the prevention of breast cancer in high-risk women based on results showing a 49% reduction in the risk of invasive breast cancer and a 50% reduction in the risk of non-invasive breast cancer compared with placebo [19].

The mixed agonist and antagonist activity of SERMs, which causes endometrial proliferation, has led to the development of compounds that have ‘pure’ anti-estrogenic effects [20]. Fulvestrant is the first compound of this class and binds to ER after it is manufactured in the cytoplasm, thus preventing its transport to the nucleus [17]. The efficacy of fulvestrant in women with advanced breast cancer who have progressed on tamoxifen suggests that it is not cross-resistant [21] and the Food and Drug Administration (FDA) have approved this agent for the treatment of hormone receptor-positive metastatic breast cancer following first-line therapy with tamoxifen.

Aromatase inhibitors are used to block the activity of the enzyme aromatase in converting androgens to estrogen in postmenopausal women [22]. Aromatase inhibitors are not suitable for use in premenopausal women because endogenous feedback mechanisms stimulate the ovaries to increase production of aromatase [1]. In addition, high endogenous production of estrogens by the ovaries is a more important pathway of estrogen production than the aromatase pathway in premenopausal women. Current third-generation oral aromatase inhibitors such as anastrozole, letrozole and exemestane are highly specific, reducing circulating estrogen levels to 1–10% of pretreatment levels [16], thereby removing the stimulus for ER activation in breast tumours. In large randomised phase III trials, anastrozole, letrozole and exemestane as second-line therapy for metastatic breast cancer following tamoxifen failure produce similar prolonged survival rates and are better tolerated than megestrol acetate. As first-line metastatic treatment, aromatase inhibitors produce objective response rates superior to tamoxifen [1, 23]. Thus, many oncologists advocate the use of aromatase inhibitors as first-line endocrine therapy in patients with ER-positive metastatic breast cancer [1, 24]. Anastrozole has also been evaluated in the adjuvant treatment of postmenopausal breast cancer, both compared to and in combination with tamoxifen in the so-called ATAC trial. Follow-up at 30 and 47 months indicated superior results for anastrozole in terms of local and distant recurrence, development of contralateral breast cancer and safety [25–27]. However, further follow-up is needed before anastrozole becomes standard therapy in postmenopausal women; other randomised trials are comparing aromatase inhibitors with tamoxifen.

In summary, various types of hormonal agents have been defined that share the ability to deprive tumour cells of ER stimulation, thereby decreasing tumour cell proliferation. The current roles of the different hormonal treatments available for breast cancer are summarised in Table 1. These agents are effective in preventing disease recurrence and in delaying disease progression in many but not all patients. Approximately 40% of patients receiving adjuvant hormonal therapy and most of those receiving hormonal therapy for metastatic disease will relapse. The causes

Table 1. The use of hormonal therapies for breast cancer according to menopausal status [1]

<table>
<thead>
<tr>
<th>Hormonal therapy</th>
<th>Premenopausal</th>
<th>Postmenopausal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian ablation</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td>Radiation</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td>SERMs</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>LHRH agonists</td>
<td>✓</td>
<td>×</td>
</tr>
<tr>
<td>Aromatase inhibitors</td>
<td>×</td>
<td>✓</td>
</tr>
<tr>
<td>Progestins</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Androgens</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>


✓, indicated; ×, not indicated; LHRH, luteinising hormone-releasing hormone; SERMs, selective estrogen receptor modulators.

Figure 1. Mechanism of action of hormonal agents. MacGregor JJ and Jordan VJ. Pharmacol Rev 1998; 50: 151–196 [75].
of resistance to hormonal therapy are not well understood. Loss of ER expression or functionality might be involved, but ER loss is believed to occur in 20% of cases at most. It is also believed that mutations in the ER might desensitise cancer cells to hormonal treatment, but again this is not thought to be a common cause of resistance. Another theory is that levels of co-factors are changed in resistant cells, but this is yet to be substantiated [28]. HER2 overexpression could also play a role. Signalling via HER2-activated growth factor pathways may contribute to hormonal resistance via ligand-independent ER activation and concomitant treatment with anti-HER2 therapy and tamoxifen might be able to overcome this problem [15].

**Rationale for and mechanism of action of trastuzumab**

In normal cells, HER2 plays a key role in cellular growth factor signal transduction and is involved in the regulation of cell growth, survival and differentiation [29]. The binding of ligands such as neuregulin [30] and the EGF-like ligands [31] to a heterodimer receptor complex that includes HER2 on the cell surface leads to activation of intrinsic protein tyrosine kinase activity and tyrosine autophosphorylation. Complex associations between HER2 and other family members and ligands allow great signal diversity [32]. Thus, different signalling cascades can be initiated by HER2 to transmit signal across the cell membrane and intracellular space to the nucleus, where gene activation causes mitogenic stimulation [33]. Downstream pathways affected by HER2 signalling include the mitogen-activated protein (MAP) kinase cascade [34], PI 3-kinase [35], which is involved in cell survival and differentiation, and src, which has many functions including a putative role in mammary tumorigenesis [36].

The HER2 receptor is encoded by a proto-oncogene and HER2 is amplified/overexpressed in 15–25% of human breast cancers [37] and is associated with malignant transformation and oncogenesis [38–40]. HER2 overexpression has also been correlated with poor clinical outcome, including reduced disease-free and overall survival, in women with node-positive and node-negative breast cancer [37, 41]. The effects of HER2 on both breast cancer development and the aggressiveness of the disease led to the development of trastuzumab [9]. Trastuzumab is a recombinant, fully humanised anti-HER2 monoclonal antibody (mAb) that selectively targets and binds with high affinity to HER2. It has been shown to inhibit the proliferation of human tumour cells that overexpress HER2 both in vitro and in vivo [42–44].

Large-scale pivotal trials have demonstrated that trastuzumab, as a single agent, is active in both pretreated and previously untreated women with HER2-positive metastatic breast cancer [10, 45]. Furthermore, in previously untreated patients, the combination of trastuzumab with chemotherapy prolongs time to progression, increases response rates and significantly improves survival in comparison with chemotherapy alone [11]. Efficacy is greater in women with more strongly HER2-positive disease (as measured by immunohistochemistry, which is probably a correlate of true gene amplification), who experience increases in survival of up to 45% when trastuzumab is added to chemotherapy as first-line therapy [46]. Coupled with this increased efficacy is a favourable tolerability profile characterised by mild-to-moderate infusion-related reactions and the absence of typical chemotherapy-related adverse events, although the occurrence of cardio-toxicity currently prevents the clinical use of trastuzumab in combination with anthracyclines [10, 45, 47].

**Interactions between ER and HER2 signalling in breast cancer**

Known estrogen-regulated genes include those encoding growth factors such as TGF-β and IGF-1, growth factor receptors and other signalling molecules, although many have yet to be identified and characterised [15]. Among the many pathways important for both tumour cell proliferation and modulation of ER activity are: HER2 signalling pathways, cell survival (PI3K or AKT) pathway, cell proliferation pathway mediated by MAP kinases ERK 1 and 2, stress-induced pathways mediated by the stress-activated protein kinase/INK and p38 MAP kinases.

Recent data suggest that these growth factors and their signalling molecules are also important for breast cancer growth and progression. Inter-relationships between these disparate molecular pathways amplify cell survival and proliferation stimuli and may also contribute to resistance to hormonal therapies [15].

**Evidence for interactions between ER and HER2 signalling pathways**

Considerable evidence from in-vitro studies supports the existence of a potential interaction or ‘cross talk’ between HER2 and ER pathways (Figure 2). The existence of an inverse relationship between ER expression and HER2 overexpression in human breast cancer has been well established in retrospective clinical studies [13]. The proportion of patients with ER/HER2-positive breast tumours is ~9%.

![Figure 2. Estrogen receptor/HER2 cross-talk](https://academic.oup.com/annonc/article-abstract/14/12/1697/166041/1699)
It has been demonstrated in vitro that estrogen down-regulates HER2 expression and that anti-estrogen produces partial reversal of this effect in MCF-7 breast cancer cells [48]. The promoter of the HER2 gene contains an estrogen response element and estrogen has been shown to suppress the transcription of HER2 [49], while tamoxifen up-regulates the transcription of HER2 [50]. Thus, the estrogen response element seems to negatively regulate HER2 transcription under the influence of estrogen binding to ER [51]. MCF-7 breast cancer cells, which are ER positive and responsive to tamoxifen, become insensitive to the growth inhibitory effect of tamoxifen, even though they remain ER positive, after transfection with the HER2 coding region [52].

The mechanism for these effects probably lies in feedback through downstream signalling molecules. HER2-transfected MCF-7 cells are resistant to tamoxifen (Figure 3) and HER2 overexpression or HER2 stimulation leads to both ER downregulation and increased ER phosphorylation and transcriptional activation [51, 53, 54]. This provides a potential mechanism for tamoxifen resistance in HER2-positive breast cancer cell lines. Furthermore, downregulation of HER2 appears to shut down the HER2-initiated MAP kinase pathways, such as Ras–MAP kinase, involved in cell cycle stimulation, and makes other cell membrane ER-linked apoptotic MAP kinase pathways such as p38 MAP kinase and JNK dominant [55]. In support of this, blocking MAP kinase using a specific inhibitor restores the inhibitory effects of tamoxifen on ER-mediated transcription in HER2-positive cells [56].

Another observation of relevance to this discussion is that tamoxifen has estrogen agonist effects and causes significant elevations of plasma oestradiol levels in most premenopausal and some postmenopausal patients [57]. Recent studies have indicated that MEKK1, a downstream mediator of HER2 signalling, activates ER and stimulates the agonist activity of tamoxifen [58]. Thus, HER2 positivity and increased downstream signalling could potentially convert tamoxifen from a breast cancer cell inhibitor into a stimulatory agent.

Finally, the ability of HER2 signalling to disrupt the tamoxifen-stimulated interaction of ER with co-repressor molecules such as N-CoR, and thus increase the transcriptional activity of ER through recruitment of co-activators that allow stimulation of gene promoters containing estrogen response elements, has been investigated [59]. This appears to occur in vitro and a HER2 tyrosine-kinase inhibitor can restore tamoxifen sensitivity [59].

In summary, preclinical data suggest that interactions between the ER and HER2 signalling pathways might be expected to result in clinical resistance of HER2-positive breast cancer to hormonal therapy. Furthermore, it is theoretically possible that women with HER2-positive, ER-positive breast cancer could have a worse prognosis with tamoxifen therapy than with no therapy due to promotion of the agonist effects of tamoxifen through HER2-stimulated signalling.

Clinical data indicating that HER2-positive breast cancer is resistant to hormonal therapy

Several clinical reports have indicated that response rates to first- or second-line therapy with tamoxifen and other anti-estrogens are lower in HER2-positive patients than those who are HER2-negative (Table 2). However, it must be noted that these studies are based on retrospective analysis and the findings need to be validated in prospective trials.

In addition, a number of studies have indicated that HER2 overexpression reduces both response duration and survival duration in patients treated with hormonal therapy [14, 60, 61]. Of note, the 20-year update of the Naples GUN Trial [62] showed that HER2 overexpression not only predicted resistance to tamoxifen, but that HER2-positive patients had a worse outcome on tamoxifen therapy than those who were untreated; a positive HER2 status was a strong predictor of tamoxifen failure independent of ER status and other major prognostic variables. Furthermore, patients with HER2-positive, ER-positive breast cancer have worse outcomes than HER2-negative patients when treated with megestrol acetate, letrozole or fadrozole [14]. Although it should be noted that some reports have failed to observe this association [63, 64], a meta-analysis has further indicated that HER2-overexpressing metastatic breast cancer is resistant to hormonal therapy, with a relative risk for disease progression of 1.41 [12]. In addition, it has been noted that the time to progression has been <6 months in patients with HER2-positive breast cancer in all trials of first-line hormonal therapy to date [65].

Limited clinical evidence suggests that the response to the aromatase inhibitor letrozole in patients with HER2-positive breast cancer may differ from that seen with tamoxifen. In a randomised study of neoadjuvant letrozole versus tamoxifen in postmenopausal patients with ER-positive and/or PgR-positive primary breast cancer ineligible for breast-conserving surgery, ER-positive, HER1-positive and HER2-positive cancers responded well to letrozole but responses to tamoxifen were infrequent [66]. Ali et al. have recently reported similar results [67]. The investigators explain this finding by suggesting that because letrozole effectively removes estrogen, ER becomes monomeric and incapable of transcriptional activity, whereas the agonist activity of tamoxifen can still be stimulated by MEKK1 [66]. However, the pooled data described above [14] and preliminary results of a
Table 2. Response rates to treatment of metastatic breast cancer with tamoxifen or other anti-estrogens according to HER2 status

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Specimen type</th>
<th>HER2 detection method</th>
<th>HER2+</th>
<th>HER2−</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicholson et al. 1990 [76]</td>
<td>61</td>
<td>Paraffin</td>
<td>IHC</td>
<td>7% (1/14)</td>
<td>38.3% (18/47)</td>
<td>NS</td>
</tr>
<tr>
<td>Wright et al. 1992 [77]</td>
<td>65</td>
<td>Paraffin</td>
<td>IHC</td>
<td>7% (1/14)</td>
<td>37% (19/51)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Leitzel et al. 1995 [78]</td>
<td>300</td>
<td>Serum</td>
<td>EIA</td>
<td>20.7% (12/58)</td>
<td>40.9% (99/242)</td>
<td>0.004</td>
</tr>
<tr>
<td>Yamauchi et al. 1997 [79]</td>
<td>94</td>
<td>Serum</td>
<td>ELISA</td>
<td>9% (3/32)</td>
<td>56% (35/62)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Elledge et al. 1998 [63]</td>
<td>204</td>
<td>Paraffin</td>
<td>IHC</td>
<td>54% (33/61)</td>
<td>57% (82/143)</td>
<td>0.67</td>
</tr>
<tr>
<td>Houston et al. 1999 [80]</td>
<td>241</td>
<td>Paraffin</td>
<td>IHC</td>
<td>38% (29/76)</td>
<td>56% (92/165)</td>
<td>0.02</td>
</tr>
<tr>
<td>Ellis et al. 2001 [66]</td>
<td>142</td>
<td>Paraffin</td>
<td>IHC</td>
<td>17% (4/23)</td>
<td>40% (48/119)</td>
<td>0.045*</td>
</tr>
<tr>
<td>Lipton et al. 2002 [14]</td>
<td>711</td>
<td>Serum</td>
<td>ELISA</td>
<td>7% (16/217)</td>
<td>20% (101/494)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Results shown are for tamoxifen. Response rates were similar for HER2-positive and HER2-negative patients who received letrozole. NS, not stated.

prospective study of second-line treatment of ER-positive or PgR-positive metastatic breast cancer with letrozole suggest that the median time to treatment failure (TTF) is shorter in HER2-positive patients than HER2-negative patients (5.6 versus 11.6 months, respectively; P = 0.005) [68]. The data are further confusing by recent results from an evaluation of the predictive value of HER2 using data from a trial of 709 women randomised to receive adjuvant surgical oophorectomy and tamoxifen: women with HER2-positive disease were more likely to benefit from the adjuvant endocrine therapy than those women with HER2-negative disease [69]. Therefore, further data are needed before firm conclusions can be made regarding whether there is a difference in the effect of HER2 status on response to tamoxifen and aromatase inhibitors.

**Preclinical evidence supporting studies of trastuzumab in combination with hormonal therapy**

As outlined above, there is significant preclinical evidence to suggest that cross-talk between HER2 and ER occurs in breast cancer cells. This appears to be due to a variety of mechanisms. A number of researchers have therefore investigated whether modifying the activity of ER and/or HER2 can alter the responsiveness of tumour cells to an anti-estrogen or to trastuzumab. Although exposure of HER2-transfected, ER-positive MCF-7 cells to tamoxifen alone did not lead to reduction or cessation of tumour growth (as shown in Figure 3), simultaneous treatment with both mAb 4D5 (the parent antibody of trastuzumab) and tamoxifen restored sensitivity to tamoxifen [52]. Similarly, the effect of treatment with trastuzumab and fulvestrant on the growth of three human breast cancer cell lines that express different levels of ER and HER2 has been investigated [70]. In ML20 cells, which express a high level of ER and a moderate level of HER2, combined treatment produced enhanced growth inhibitory effects. However, no additive effects were seen in KPL-4 cells, which express no ER and a moderate level of HER2, or in MDA-MB-231 cells, which express no ER and a low level of HER2 (Figure 4) [70]. In addition, the combination of tamoxifen and mAb 4D5 has been shown to produce greater inhibitory effects on cell proliferation than either agent alone in ER-positive BT474 cells, in which HER2 is naturally amplified [52, 71]. These data are particularly important because a tumour cell line that has naturally developed HER2 amplification and is also ER-positive would be expected to be dependent on the activity of these receptors. The observation that inhibiting both receptors has greater growth inhibitory effects than inhibiting either one suggests that combining trastuzumab with hormonal therapy could represent a rational approach for clinical evaluation.

Clinical data from the trastuzumab trial programme also suggest that trials of trastuzumab in combination with hormonal therapy are warranted. A retrospective analysis of women with ER-positive and ER-negative breast cancer enrolled in trastuzumab clinical trials has indicated that women with ER-negative/HER2-positive disease and ER-positive/HER2-positive disease had similar clinical outcomes when treated with trastuzumab alone or trastuzumab plus chemotherapy [72]. In addition, prior therapy with hormonal agents did not influence the degree of clinical benefit from first-line trastuzumab therapy [72].

Together, these preclinical and clinical observations indicate that ER-positive, HER2-positive breast tumour cells respond to trastuzumab but are resistant to hormonal therapies such as tamoxifen. However, trastuzumab restores the sensitivity of ER-positive, HER2-positive cells to tamoxifen and fulvestrant. Furthermore, the observation that women with ER-negative/HER2-positive breast cancer, which would be expected to be more aggressive than ER-positive/HER2-positive breast cancer, obtain similar benefit from trastuzumab therapy could indicate that treating ER-positive/HER2-positive breast cancer with trastuzumab plus hormonal therapy will produce additional benefits in this population.

**Application in clinical practice**

As previously discussed, patients with ER-positive/HER2-positive disease are less likely to respond to tamoxifen than women with ER-positive/HER2-negative disease. Randomised clinical trials
have been designed to examine various aspects of combining trastuzumab with hormonal therapy in women with ER-positive/HER2-positive metastatic breast cancer. The rationale for combining trastuzumab plus tamoxifen in a phase II clinical trial in patients with ER-positive, HER2-positive or HER2-negative recurrent or metastatic breast cancer has been reported [73]. This rationale is based on the hypothesis that trastuzumab will reverse the resistance to tamoxifen that may develop in ER-positive breast cancer.

Other trials are examining the potential of combining trastuzumab with aromatase inhibitors. Although data regarding the effects of interactions between ER and HER2 in patients with ER-positive, HER2-positive breast cancer treated using aromatase inhibitors are less clear, they are widely used as an alternative to tamoxifen as first-line hormonal therapy for patients with metastatic breast cancer and have proven efficacy in this setting [74]. A phase II/III randomised, controlled, open label trial of anastrozole with or without trastuzumab is being conducted in 202 patients with ER-positive/HER2-positive and/or PgR-positive advanced metastatic breast cancer. This international study will recruit patients from more than 140 centres; to date, more than 70 patients have been enrolled. Of note, patients can have received anastrozole up to 4 weeks prior to study entry and patients randomised to the anastrozole-alone arm can receive trastuzumab upon progression. Anastrozole is administered 1 mg p.o. daily, and trastuzumab as a 4 mg/kg loading dose followed by 2 mg/kg weekly thereafter until disease progression. The primary aim of this study is to evaluate progression-free survival (PFS), which will be assessed with a log-rank test. There are no data on PFS of HER2-positive breast cancers treated with anastrozole. Therefore, the sample size for this study is based on the demonstrated time to progression in phase III trials of anastrozole in patient populations that have not been preselected for HER2 status and will achieve 80% power at a two-sided significance level of 5%, assuming that 187 events are seen. Secondary objectives include evaluation of safety, comparison of the overall clinical benefit rate between the two arms, and evaluation of overall survival, response and 2-year survival in the two treatment arms. Moreover, several trials of letrozole with or without trastuzumab are also being conducted. The largest of these is enrolling 300 patients from 80 centres and will investigate letrozole with or without trastuzumab as first-line therapy for patients with ER-positive/HER2-positive metastatic breast cancer. The primary end point is time to progression and the study is powered to show a 33% reduction in risk of progression for trastuzumab plus letrozole versus letrozole alone; secondary end points include objective tumour response rate, TTF and overall survival. Thus, a range of clinical trials are now ongoing to determine whether the addition of trastuzumab to hormonal treatments will provide patients with clinical benefits.

**Conclusions**

In conclusion, the evidence that HER2 overexpression is correlated with poor clinical outcome, the existence of cross-talk between the HER2 and ER signalling pathways in breast cancer, and the lack of benefit achieved with hormonal therapy in patients with ER-positive/HER2-positive disease, and hence the fact that these patients are receiving sub-optimal treatment, suggest that combining treatments that target these different pathways may provide additional clinical benefits for patients with breast cancer.

Trastuzumab has produced significant survival improvements in combination with chemotherapy in the first-line treatment of HER2-positive metastatic breast cancer and has also shown activity as a single agent as first- or second-line therapy. Tamoxifen has been shown to produce clear benefits in terms of survival and prevention of recurrence for both premenopausal and postmenopausal women with ER-positive breast cancer. Recent studies of aromatase inhibitors have demonstrated superior objective responses in comparison with tamoxifen. Taken together the evidence suggests that targeted non-chemotherapeutic combinations of trastuzumab with hormonal therapy, which are currently being

![Figure 4. Growth inhibitory effects of ICI 182, 780 alone, 10 µg ml⁻¹, Herceptin® alone or their combination in ML20 cells (A), KPL-4 cells (B) or MDA-MB-231 cells (C). The cells were incubated with medium containing the reagents for 4 days and counted with a Coulter counter. The values represent the percentages of the control and means of triplicate samples. Bars = SEM. *P < 0.05 versus control, **P < 0.01 versus control. Adapted with permission from Kunisue H et al. Br J Cancer 2000; 82: 46–51 [70].](https://academic.oup.com/annonc/article-abstract/14/12/1697/166041)
studied in large-scale clinical trials, represent the future of cancer therapy, allowing the individualisation of treatment based on tumour characteristics.

References


