Role of biologic therapy and chemotherapy in hormone receptor- and HER2-positive breast cancer

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Background: To review the efficacy of chemotherapy and human epidermal growth factor receptor 2 (HER2)-targeted therapy when used in addition to hormonal therapy for the optimal management of estrogen receptor-positive (ER+) human epidermal growth factor receptor 2-positive (HER2+) breast cancer.

Design: Literature published from January 2003 to March 2008 was reviewed to assess the use of chemotherapy and biologic therapy in addition to hormonal agents.

Results: Aromatase inhibitors (AIs) demonstrated greater effectiveness in the adjuvant setting than tamoxifen for the management of ER+ and HER2+ breast cancer. Evidence of cross talk between HER2- and ER-signaling pathways suggests that combined treatment with HER2 blockade and hormonal therapy may offer clinical advantages beyond those provided by hormonal therapy alone in ER+/HER2+ disease. Combined therapy with trastuzumab plus an aromatase AI significantly improves progression-free survival, response rates, and clinical benefits when compared with AI monotherapy in postmenopausal women. Several large studies demonstrated that trastuzumab significantly improves disease-free and overall survival when given in combination with, or following, chemotherapy, regardless of hormone receptor status.

Conclusions: HER2-targeted therapy maybe combined with AIs for the treatment of ER+/HER2+ metastatic breast cancer in postmenopausal women. HER2-targeted therapy in combination with AIs for treatment of ER+/HER2+ early breast cancer needs to be prospectively evaluated.

Key words: aromatase inhibitor, breast cancer, chemotherapy, estrogen receptor, HER2, trastuzumab

introduction

Approximately 75% of all invasive breast tumors are hormone receptor positive [estrogen receptor positive (ER+) or progesterone receptor positive (PR+)] [1]. As estrogen plays a critical role in the development and progression of such cancers [2, 3], the ER has long represented an important target for endocrine (or hormonal) therapies that aim to block the action of estrogen on the tumor cells [1, 4, 5]. Two major types of hormonal therapy are currently available for the treatment of hormone receptor-positive breast cancer: antiestrogens (e.g., tamoxifen), which prevent the interaction of estrogen with its cognate receptor, and the aromatase inhibitors (AIs; e.g., letrozole, anastrozole, and exemestane), which block the final enzymic step in the biosynthesis of estrogen and thus inhibit estrogen production [3, 4, 6].

Tamoxifen is an established hormonal therapy for reducing recurrence and mortality rates in women with estrogen-dependent breast cancer, irrespective of patient age, menopausal status, and disease stage [2, 7, 8]. Data from prospective, randomized trials indicate that it can be used effectively for up to 5 years in the adjuvant setting [4, 8, 9]. However, the use of tamoxifen maybe complicated not only by potential tumor resistance and patient refractoriness to treatment but also by the drug’s weakly estrogenic effects, which can lead to reduced clinical efficacy and an increased risk of stroke and endometrial cancer [4, 6].

The development of third-generation AIs (e.g. letrozole, anastrozole, and exemestane) has provided an alternative to tamoxifen treatment in the management of postmenopausal women with ER+ breast cancer. Unlike tamoxifen, AIs have no ER agonist activity. Furthermore, their differing mode of action may overcome tamoxifen resistance [4, 6]. Recent data support the use of AIs as initial adjuvant therapy, as sequential therapy following 2 to 3 years of tamoxifen or as extended therapy following up to 6 years of tamoxifen treatment [8, 10, 11], while several large-scale studies of postmenopausal women with early-stage breast tumors show that AIs demonstrate superior efficacy and tolerability profiles when compared with tamoxifen in the adjuvant setting [12–14].

Guidelines from the National Comprehensive Cancer Network recommend the use of adjuvant hormonal therapy in...
the majority of hormone receptor-positive breast cancers, regardless of menopausal status, patient age, or the human epidermal growth factor receptor 2 (HER2) status of the tumor [8]. Currently, there is uncertainty regarding the optimal treatment of early-stage, ER+/human epidermal growth factor receptor 2-positive (HER2+) disease, particularly in patients with tumors <1 cm and axillary node-negative disease. The selection of an optimal therapeutic strategy is further hindered by inconclusive or inconsistent data from studies that aim to determine whether ER+/HER2+ tumors are sufficiently sensitive to hormonal therapy [8]. In addition, there exists a widespread perception that chemotherapy has only modest beneficial effects in patients with hormone receptor-positive breast cancer and that these benefits are restricted to women with highly proliferative lesions or to those who do not receive adjuvant hormonal treatment [1].

Reviews of the literature, using Medline, and a review of abstracts, from breast cancer and oncology meetings, were carried out to identify relevant publications on HER2+, hormone receptor-positive breast cancer. This article assesses the value of chemotherapy and HER2-targeted biologic therapy when used as additional treatments for the optimal management of these patients.

relationship between the ER- and HER2-signaling pathways

HER2 and the ER coactivator, AIB1, are often overexpressed together in ER+ breast tumors [15], and evidence obtained from studies of human breast cancer cell lines has revealed the presence of bidirectional cross talk between the HER2 and ER signal transduction pathways [4, 15, 16]. The importance of these interactions was highlighted in an early study by Read et al. [17], who demonstrated that estrogen can modulate HER2 proto-oncogene expression. In human breast cancer MCF-7 cell lines, which contain high concentrations of ER, the addition of estrogen reduced levels of HER2 messenger RNA and protein by 60% and 50%, respectively, in a dose-dependent manner [17].

The importance of the direct link between the HER2 and ER pathways is further highlighted by observations that the HER2-signaling network may affect the sensitivity of estrogen-dependent tumors to antiestrogen therapy. The introduction of a HER2 expression vector or HER2 complementary DNA to ER+ human breast carcinoma cell lines can increase the malignant phenotype of tumor cells, stimulate estrogen-independent growth, and induce development of resistance to tamoxifen [18, 19]. These phenomena may all be facilitated by HER2-mediated mitogen-activated protein kinase signaling [20].

evidence of resistance to hormonal therapy in HER2+ tumors

Further evidence for interaction between the HER2- and ER-signaling pathways comes from studies in which patients with HER2-overexpressing, ER+ breast tumors demonstrate resistance to hormonal therapy. In a study of women receiving daily tamoxifen for the initial treatment of advanced, ER+ breast cancer, 50% of all HER2-amplified tumors had lower ER levels (<50 fmol/mg protein), compared with 28% of non-HER2-amplified tumors (P = 0.02) [21]; HER2 amplification was also associated with a moderately reduced response to tamoxifen treatment (Table 1) [16, 21]. Lipton et al. reported similar findings: response to second-line hormonal therapy with megestrol acetate or an AI (fadrozole or letrozole) was significantly reduced among patients with metastatic ER+ breast tumors and elevated HER2 serum levels, as were time to progression (TTP), time to treatment failure (TTF), and duration of survival (Table 1) [16, 21].

As part of a phase III, neo-adjuvant trial of tamoxifen versus letrozole by Ellis et al. [22], tumor samples were analyzed at baseline and study end to quantify the proliferation marker, Ki67. This marker gives an indication of the effectiveness with which hormonal therapy inhibits estrogen-dependent cell cycling. The analysis found that letrozole demonstrated advantages over tamoxifen in both the HER1 (EGFR)/1–2 subset (86% versus 79% reduction in Ki67; P = 0.0149) and the HER1/2+ subset (88% versus 45%; P = 0.0018). The findings suggested that HER1/2+ tumors show some resistance to tamoxifen and that HER1/2 status does not influence the antiproliferative effect of letrozole in women with ER+, locally advanced breast cancer.

In an extension of this study, which included an additional 106 samples, Ellis et al. [23] reported that the clinical response to neo-adjuvant letrozole therapy was not adversely affected by HER2 status (71% in patients with either HER2+ or HER2– tumors), suggesting that HER2+ tumors are sensitive to

Table 1. Response to hormonal therapy in patients with ER+ breast cancer and elevated HER2 levels in tissue and plasma: summary of data from two studies

<table>
<thead>
<tr>
<th></th>
<th>First-line tamoxifen [21]</th>
<th>Second-line megestrol acetate, fadrozole, or letrozole [16]</th>
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<tbody>
<tr>
<td></td>
<td>Normal HER2 (n = 104)</td>
<td>HER2 amplified (n = 32)</td>
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<tr>
<td>Overall response rate (%)</td>
<td>56</td>
<td>47</td>
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<tr>
<td>TTP</td>
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<td>–</td>
</tr>
<tr>
<td>TTF</td>
<td>7 months</td>
<td>5 months</td>
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<tr>
<td>Median survival (months)</td>
<td>31</td>
<td>25</td>
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Response was defined as complete response, partial response, or stable disease for 26 months.

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; TTP, time to progression; TTF, time to treatment failure.
short-term estrogen deprivation. They demonstrated that most HER2– tumors showed significant reductions in Ki67 levels following letrozole or tamoxifen treatment ($P = 0.0001$ for both) (Figure 1A and C) [23] and the HER2+ group showed a blunted response in Ki67 levels following letrozole or tamoxifen treatment that was not statistically significant (Figure 1B and D) [23]. This suggested that the ER+, HER2+ and ER+, HER2– tumors respond similarly to letrozole at a clinical level. This is in contrast to reports that ER+, HER2+ tumors are less sensitive to letrozole and other endocrine therapies [23]. However, in examining the relationship between cell cycle complete response (total clinical disappearance of cancer) and HER2 gene amplification in tumors treated with letrozole, 88% of HER2+ tumors were resistant to ongoing hormonal therapy [23]. These findings provide further confirmation that HER2 gene amplification reduces the antiproliferative effects of hormonal therapy and thus induces therapeutic resistance that may become apparent later in the course of the disease.

The TransATAC study is an ongoing, retrospective subanalysis of data from the larger-scale, double-blind, Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial. In the ATAC trial, 9366 postmenopausal patients with primary ER+ and/or PR+ breast cancers were treated with anastrozole or tamoxifen, or combination treatment, for 5 years [12]. The TransATAC study was designed to examine the effect of HER2 status on disease recurrence in these patients [24]. At the time of reporting, 1856 tumor blocks had been collected and analyzed. The investigators reported that patients with tumors that exhibited HER2 positivity had significantly shorter time to disease recurrence in both the anastrozole [hazard ratio (HR) 3.23; $P < 0.0001$] and tamoxifen (HR 3.23; $P < 0.0001$) treatment groups. Further analysis of data from patients with HER2+ disease treated with anastrozole revealed that there was no evidence of a superior clinical benefit (CB) compared with patients with HER2-negative disease. The prognostic significances of ER, PR, and HER2 statuses were similar for patients treated with tamoxifen or anastrozole.

This observation was consistent with findings from the Breast International Group 1-98 Collaborative Study [13], in which postmenopausal women with operable, invasive, ER+ breast cancer received adjuvant letrozole or tamoxifen monotherapy for 5 years, letrozole for 2 years followed by tamoxifen for 3 years, or tamoxifen for 2 years followed by letrozole for 3 years. Analyses were carried out to investigate whether letrozole or tamoxifen treatment resulted in superior outcomes in patients with HER2+ disease. A CB of letrozole over tamoxifen was demonstrated; however, HER2 status did not affect the clinical outcome [25].

Results from other studies also fail to show any evidence of an interaction between HER2+ tumor status and hormonal therapy. A large-scale, randomized, prospective study that assessed 1 year of adjuvant tamoxifen in 1716 high-risk, postmenopausal women with breast cancer found that HER2 status could not be used to independently predict response or resistance to tamoxifen [26]. The study investigators found no evidence that HER2+ tumor status could predict tamoxifen resistance. Patients with HER2– tumors were found to have similar disease-free survival (DFS) as patients with low-positive tumors. However, they also conceded that the study did not have sufficient statistical power to determine conclusively whether a small group of patients with hormone receptor-positive tumors would be resistant to, or have a detrimental response to, tamoxifen therapy.

Investigators who conducted the CALGB 8541 trial reported similar results [27]. Among 651 pre- and postmenopausal women receiving adjuvant tamoxifen for the treatment of ER+/HER2+ early-stage breast cancer, the estimated reduction in risk of disease recurrence or death was 32% in patients with HER2 overexpression and 39% in those with normal HER2 expression. The estimated reductions in the risk of death were 36% and 30% for patients with HER2 overexpression and normal HER2 levels, respectively. No evidence of an interaction between HER2 and tamoxifen was found, and the authors of the report concluded that the CBs of tamoxifen in patients with ER+ early breast cancer were not dependent on HER2 status.

**use of HER2-targeted biologic therapy with hormonal therapy**

As ~50% of HER2+ tumors are also ER+ [28–30], the relationship between these two signaling pathways would

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**Figure 1.** Geometric mean levels of Ki67 measured in breast tumors before (dark gray bars) and after (light gray bars) treatment with either letrozole or tamoxifen treatment. Tumors A and C were HER2– and tumors B and D were HER2+. [23]. HER2, human epidermal growth factor receptor 2. Adapted from Ellis et al. [23].
appear to offer an attractive therapeutic target. The previous section of this article described how the efficacy of hormonal therapy in HER2+ breast cancer has yet to be fully defined in the clinical setting; however, there is evidence to support the use of a combined treatment approach using hormonal therapy and HER2-targeted biologic therapy (e.g. trastuzumab or lapatinib) in women with ER+/HER2+ disease. This evidence comes from studies such as that reported by Sabnis et al. [31], who used a mouse model of human ER+ breast cancer to assess the mechanisms of loss of sensitivity to letrozole. A long-term letrozole treated-cell line (LTLLT-Ca) isolated from letrozole-refractory tumors was developed and treated with the HER2-targeted, humanized mAb, trastuzumab (Genentech, Inc., San Francisco, CA). Trastuzumab treatment inhibited the growth of the LTLLT-Ca cells in a dose-dependent manner; in addition, pretreatment of LTLLT-Ca cells with trastuzumab restored their responsiveness to letrozole therapy. When trastuzumab was used with an antiestrogen therapy or AI, the combination was found to be significantly more effective in reducing tumor growth than any of these therapies used alone (P < 0.001). This suggests that such a strategy maybe useful for both reversing and prolonging the onset of resistance to hormonal therapies.

Preclinical work with lapatinib also supports the use of HER2-targeted therapy to increase responsiveness to treatment with hormonal therapy. Using cell models of endocrine resistance, Leary et al. [32] et al. found that the sensitivity of the cell models to 4-hydroxy-tamoxifen was increased when lapatinib was added. Similar synergistic effects were also reported from a study using lapatinib in combination with fulvestrant in four cell lines with varying HER2, ER-alpha, and HER1/EGFR receptor status [33].

Further support for a combination approach to the treatment of ER+/HER2+ breast tumors was provided by a clinical study in which 562 women with ER+ metastatic breast cancer (MBC) were treated with first-line letrozole or tamoxifen [34]. Clinical responses were stratified in accordance with serum HER2 levels. Significantly greater objective response rate (ORR), CB, longer TTP, and TTF were seen with letrozole only in patients with normal levels of HER2. In patients with elevated serum HER2/neu, no significant difference was noted between letrozole and tamoxifen; however, patients treated with letrozole showed a trend favoring longer TTP and TTF. These results prompted the authors to conclude that patients with ER+/HER2+ MBC might benefit from greater growth inhibition achieved by combined blockade of both the ER and HER2 pathways.

In response to these and similar findings, trials assessing combined treatment with trastuzumab and hormonal therapy have been conducted. In a recent phase II trial, 31 women with ER+ and/or PR+ and HER2+ advanced breast cancer received trastuzumab and letrozole as first- or second-line therapy until disease progression or unacceptable toxicity [29]. ORRs were similar between the overall population and the subset of patients (n = 25) who had tumors that demonstrated HER2 gene amplification using fluorescence in situ hybridization and/or overexpressed the HER2 protein (26% and 24%, respectively) as was median TTP (3.8 and 5.5 months, respectively). Durable responses (≥21 year) were obtained in at least one-quarter of patients. The authors concluded that although the response rate obtained in this study was similar to that obtained for trastuzumab monotherapy in another trial by Vogel et al. [35], the durability of responses maybe increased when trastuzumab and letrozole are used in combination (5.5 to 5.8 months in this study compared with 3.5 months in the study by Vogel et al.).

In the randomized, controlled, open-label, multicenter, phase II TAnDEM trial, the efficacy of trastuzumab plus anastrozole was compared with anastrozole alone in 207 postmenopausal women with HER2+ and ER+ and/or PR+ MBC [28]. The combination therapy regimen produced significantly greater improvements in progression-free survival, response rate, TTP, and CB rate than anastrozole alone; overall survival (OS) was also longer in patients receiving trastuzumab plus anastrozole, despite the crossover of >50% of patients from the anastrozole monotherapy group to the combination therapy group following disease progression (Table 2) [28].

The data from these trials strongly indicate that blockade of the HER2 pathway is a valid therapeutic option for women with ER+/HER2+ breast tumors and that trastuzumab can be used in combination with hormonal therapy to improve outcomes in these women. An area that remains in need of further research, however, is the use of adjuvant trastuzumab in combination with hormonal therapy for the treatment of patients with no nodal involvement and a primary tumor that is <1 cm. At the present time, the role of trastuzumab in the treatment of these patients has not been defined adequately [36].

In addition to the numerous trastuzumab studies that have been conducted to date, phase III trials of lapatinib in combination with hormonal therapy have also been initiated. These include study EGF3008, which will compare the efficacy of letrozole plus lapatinib combination therapy with letrozole alone in women with hormone receptor-positive, advanced breast cancer or MBC.

**chemotherapy in hormone receptor-positive breast cancer**

Favorable data obtained from several recent studies contest the perception of chemotherapy as being beneficial only in a small subset of patients with highly proliferative tumors and/or those who do not receive adjuvant hormonal therapy. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B20 trial, women with ER+ tumors that carried a high risk of recurrence

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<th>Table 2. Efficacy data from the TAnDEM trial [28]</th>
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<td>Progression-free survival (months)</td>
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<td>Clinical benefit rate (%)</td>
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<td>Time to progression (months)</td>
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<td>Overall survival (months)</td>
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<sup>a</sup>Based on 147 assessable patients.
[defined as those with a gene recurrence score (RS) ≥51] derived a large benefit from the addition of chemotherapy to tamoxifen treatment, with 10-year Kaplan–Meier estimates for freedom from distant recurrence improving from 60% to 88% [37]. The benefit from the addition of chemotherapy to tamoxifen treatment were not seen in those patients who carried an intermediate risk (RS 18–30) or low-risk RS <18) [37].

Results from a randomized, controlled, phase II trial comparing the efficacy of AIs (anastrozole or exemestane) with that of chemotherapy in the neo-adjuvant treatment of ER+ and/or PR+ breast cancers showed that the two treatments had similar clinical efficacy [38]. Clinical objective response was ~64% for both treatment arms, while the median times to clinical response were 57 and 51 days for patients treated with aromatase inhibition and chemotherapy, respectively (P = not significant). In addition, rates of pathologic complete response (3% for AIs and 6% for chemotherapy) and disease progression (9% for both groups) did not differ significantly between the two groups, suggesting that chemotherapy provides equivalent efficacy to that offered by AIs in the neo-adjuvant setting.

The Adjuvant Breast Cancer Trials Collaborative Group examined the effects of ovarian ablation or suppression in pre- and perimenopausal patients with early breast cancer who were receiving prolonged tamoxifen (5 years) with or without chemotherapy [39]. They found that ovarian ablation or suppression does not add to the benefits of prolonged tamoxifen in premenopausal women who are also receiving chemotherapy. However, they reported the possibility that a subgroup of premenopausal patients with ER+ tumors, who did not receive chemotherapy, could benefit from the addition of ovarian ablation or suppression [39]. This was observed from a study by Love et al. [40]. They reported that combined surgical oophorectomy and tamoxifen are effective as adjuvant therapy in premenopausal women with hormone receptor-positive tumors. The 5-, 7-, and 10-year Kaplan–Meier curves for DFS were 83%, 82%, and 66%, respectively, for ER+ patients [40]. In addition, the 5-, 7-, and 10-year Kaplan–Meier curves for OS were 87%, 84%, and 80%, respectively, for ER+ patients [40].

use of trastuzumab and chemotherapy in ER+/HER2+ disease

A growing body of evidence also suggests that hormone receptor status does not affect the efficacy of chemotherapy regimens when combined with trastuzumab for the treatment of HER2+ disease. For instance, in a retrospective analysis of HER2-overexpressing tumor samples from 596 patients enrolled in three clinical trials of MBC, ORRs and TTP showed greater improvements in patients treated with trastuzumab plus chemotherapy than in those treated with chemotherapy alone, irrespective of hormone receptor status (Figure 2) [41].

Similar results were obtained in studies of patients with early breast cancer, such as the large-scale NSABP trial B-31 and the North Central Cancer Treatment Group (NCCTG) trial N9831 [42]. In the joint analysis of NSABP B-31 and NCCTG N9831, the addition of trastuzumab to adjuvant chemotherapy significantly improved DFS by 52% [HR 0.48; 95% confidence interval (CI) 0.41–0.57; P < 0.00001] and OS by 35% (HR 0.66; 95% CI 0.51–0.84; P = 0.0007) after a median of 4-year follow-up when compared with chemotherapy alone. The differences in absolute benefits between the two treatment arms were similar for patients with hormone receptor-positive and negative disease (81.7% and 89.4% in the trastuzumab-containing arm for hormone receptor-negative and hormone receptor-positive disease, respectively). Furthermore, in the Herceptin Adjuvant (HERA) trial, 1 year of trastuzumab treatment following standard adjuvant chemotherapy significantly improved both DFS (HR 0.64; 95% CI 0.54–0.76; P < 0.00001) and OS (HR 0.66; 95% CI 0.47–0.91; P = 0.0115) after a median of 2-year follow-up when compared with observation [43]. Again, these benefits were observed regardless of the patients’ hormonal status. Finally, in a randomized trial assessing neo-adjuvant chemotherapy with or without concurrent trastuzumab in women with HER2+ disease, the pathologic complete response rate among all patients in the combined therapy arm was 60% (95% CI 43.3–74.3) [44]. Pathologic responses were significantly enhanced by the addition of trastuzumab, in patients with either ER− or ER+ disease. There were no recurrences among patients who received concurrent trastuzumab, and the estimated DFS at 1

![Figure 2. Overall response rate (A) and median time to progression (B) according to hormone receptor status following treatment with trastuzumab plus chemotherapy or chemotherapy alone in patients with HER2+ MBC [41]. HER2, human epidermal growth factor receptor 2; HR+, hormone receptor positive; HR−, hormone receptor negative. Reproduced with permission from Brufsky et al. [41].](https://academic.oup.com/annonc/article-abstract/20/6/993/191339)
biologic therapy should be integral to the treatment of HER2 and the association between this cross talk and resistance to hormonal therapy have prompted research into combination regimens that target both of these pathways to improve outcomes over aromatase inhibition alone.

Several large-scale studies support a role for trastuzumab in such combination therapies. Using trastuzumab in combination with hormonal agents enhances their antiproliferative effects; in postmenopausal women with metastatic disease, adding trastuzumab to AI therapy results in a longer TTP and a higher CB rate than those achieved using AI therapy alone. These findings suggest that HER2-targeted, biologic therapy should be integral to the treatment of HER2+ disease and that aromatase inhibition should be combined with trastuzumab in the treatment of postmenopausal women with ER+/HER2+ breast cancer. Additional research is, however, required to define the role, if any, for trastuzumab in the treatment of patients with ER+, axillary node-negative disease, and a primary tumor <1 cm. The benefits offered by trastuzumab are also apparent when it is used either sequential to or concurrently with adjuvant or neo-adjuvant chemotherapy regimens—an observation that contradicts the widespread perception of chemotherapy as a minimally effective treatment strategy for ER+/HER2+ breast tumors.

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**references**


