HER-2-Positive Metastatic Breast Cancer: Optimizing Trastuzumab-Based Therapy

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Abstract
Trastuzumab with a taxane as first-line therapy is now the standard of care for patients with human epidermal growth factor receptor 2 (HER-2)-positive metastatic breast cancer (MBC). The search for additional and more effective trastuzumab-based therapies continues. Novel combinations of trastuzumab with chemotherapeutic agents, including vinorelbine, gemcitabine, and capecitabine, and hormonal therapy agents, such as tamoxifen and aromatase inhibitors, are currently under investigation in clinical trials. Available data suggest these combinations will provide additional treatment options that may ultimately lead to better outcomes for patients with HER-2-positive MBC. Evidence is growing for the use of trastuzumab treatment beyond disease progression and retreatment after (neo)adjuvant relapse is being explored to assist in clinical decision making. Already, the use of trastuzumab in the metastatic setting has changed HER-2-positive status from a marker of poor prognosis to one of better overall outcome, and ongoing studies should expand further the treatment options for patients with HER-2-positive MBC. The Oncologist 2006;11(suppl 1):34–41

Introduction
Human epidermal growth factor receptor 2 (HER-2) is a transmembrane receptor tyrosine kinase with a key role in normal cell growth and differentiation. Overexpression of HER-2, usually as a result of her-2 gene amplification, can result in malignant transformation of cells and is seen in tumor tissue in up to 30% of patients with metastatic breast cancer (MBC) [1–5]. HER-2 overexpression is usually associated with a more aggressive tumor phenotype, and women with HER-2-positive disease have a poor overall prognosis and faster relapse times at all stages of cancer development [1, 6, 7]. The advent of trastuzumab (Herceptin®, F. Hoffmann-La Roche, Basel, Switzerland), a humanized monoclonal antibody against the extracellular domain of HER-2, represented a major breakthrough in the treatment of women with HER-2-positive MBC. Pivotal trials of trastuzumab alone or in combination with taxanes have resulted in significant clinical benefit [8–11], and trastuzumab plus taxanes as first-line therapy is now the standard of care for patients with HER-2-positive disease. In order to further improve patient care, the search for even more effective trastuzumab-based therapies continues in preclinical research and within clinical trials.

Pivotal Trastuzumab Trials in MBC
The pivotal randomized combination trials of trastuzumab (H0648g and M77001) demonstrated that trastuzumab plus a taxane is associated with a clinical benefit that is superior to that of a taxane alone [9, 11].

Four hundred sixty-nine HER-2-positive MBC patients who had not received prior treatment for advanced disease were enrolled in the H0648g trial. Patients who had previously received anthracyclines in the adjuvant setting or who were not suitable to receive anthracyclines (n = 188) were randomized to receive paclitaxel with or without...
trastuzumab. All other patients ($n = 281$) were randomized to receive an anthracycline plus cyclophosphamide with or without trastuzumab. The combination of trastuzumab with paclitaxel or with an anthracycline plus cyclophosphamide improved all clinical end points over paclitaxel or an anthracycline plus cyclophosphamide alone (median follow-up, 30 months). The overall survival duration was longer (22.1 vs. 18.4 months) with trastuzumab plus paclitaxel and with trastuzumab plus an anthracycline plus cyclophosphamide (26.8 vs. 21.4 months) [9]. Despite these improvements in survival, the number of cardiac events reported in that trial was higher than anticipated from initial clinical data. A retrospective analysis revealed that trastuzumab-associated cardiac events mainly occurred with concomitant use of anthracyclines. Of patients receiving trastuzumab plus an anthracycline plus cyclophosphamide, 28% experienced a cardiac event, compared with only 9.6% receiving an anthracycline plus cyclophosphamide alone [12]. As a result of this finding, the combination of trastuzumab with an anthracycline plus cyclophosphamide is not currently indicated for clinical use. Of patients receiving trastuzumab plus paclitaxel, 13% experienced a cardiac event, compared with 1% receiving paclitaxel alone. This combination is now indicated for use in a number of countries worldwide. In the pivotal trial, trastuzumab plus paclitaxel resulted in a higher objective response rate, 49% versus 17%, and longer time to progression (TTP) and response duration (RD), 6.9 versus 3.0 months and 10.5 versus 4.5 months, respectively [9]. Notably, a subset analysis revealed that trastuzumab plus paclitaxel improved outcomes in patients with immunohistochemistry (IHC) 3+ disease relative to the overall patient population (IHC 2+ and 3+). The median survival time in patients with IHC 3+ disease was 18 months without trastuzumab and 25 months with trastuzumab [13].

The M77001 trial investigated the combination of standard weekly trastuzumab plus weekly or 3-weekly docetaxel in 188 patients with previously untreated MBC. At a 24-month follow-up, the median overall survival time was 22.7 months with docetaxel alone and 31.2 months with trastuzumab plus docetaxel ($p = .0062$), despite a 57% documented crossover. All clinical outcomes investigated, including the median RD (11.4 vs. 5.1 months) and median TTP (10.6 vs. 5.7 months), were superior for trastuzumab plus docetaxel versus docetaxel alone. Only one patient receiving trastuzumab plus docetaxel experienced symptomatic heart failure (1%). Another patient experienced symptomatic heart failure 5 months after discontinuation of trastuzumab because of disease progression and following treatment with an investigational anthracycline for 4 months [11].

Both pivotal trials demonstrated a favorable safety profile for the combination of trastuzumab with a taxane. The addition of trastuzumab did not significantly add to the toxicity profile of taxanes alone.

**Novel Trastuzumab–Chemotherapy Combinations**

There is continuing interest in new trastuzumab–chemotherapy combinations, arising from the ongoing aim of improving treatment efficacy. Also, taxanes are increasingly being used in the adjuvant setting, and trastuzumab-based treatment options are needed for patients with MBC who are not candidates for taxane-containing regimens. Combinations of trastuzumab (standard schedule, 4 mg/kg loading dose followed by 2 mg/kg weekly) with agents such as vinorelbine, gemcitabine, and capecitabine have been investigated with encouraging results. Trastuzumab has also been investigated with chemotherapy combinations, including capecitabine and docetaxel, and taxanes and platinum agents.

**Trastuzumab Plus Vinorelbine**

Phase II trials of trastuzumab plus vinorelbine as first- or subsequent-line therapy indicate that this combination is highly active in the treatment of MBC, with response rates in the range of 43%–85% (Fig. 1) [14–22]. In general, first-line therapy produced higher response rates. One single-center study allowed more direct comparison of first-line (84% response rate, 34 weeks TTP) and second- or third-line therapy (67% and 16 weeks, respectively) [16], indicating that first-line therapy with this combination may be more effective than later treatment. The combination of trastuzumab with vinorelbine was well tolerated in all of these trials. There was no evidence that this combination resulted in more cardiac events compared with trastuzumab alone. For example, in the aforementioned single-center...
study, only three of 40 patients experienced grade 2 cardiac toxicity (>20% decline in left ventricular ejection fraction [LVEF] or to <50%) and no patients had symptomatic heart failure [16].

**Trastuzumab Plus Gemcitabine**

The combination of trastuzumab with gemcitabine in patients with HER-2-positive MBC has also been reported as effective and well tolerated. In a study conducted by the Hellenic Cooperative Oncology Group (HeCOG) [23], 28 patients with HER-2-positive disease received trastuzumab plus gemcitabine (1,000 mg/m² on days 1, 8, and 15) as salvage treatment after failure of prior chemotherapy with at least one taxane- and/or anthracycline-containing regimen. The overall response rate was 36%, median TTP was 7.8 months, and median overall survival time was 18.7 months (median follow-up, 17.2 months). Similarly, in a phase II study of trastuzumab plus gemcitabine (1,200 mg/m² on days 1 and 8 every 3 weeks) in MBC patients who had previously received a taxane- and/or anthracycline-containing regimen, the overall response rate in evaluable patients (n = 61) was 38%. The median RD was 5.8 months, median overall survival time was 14.7 months, and median TTP was 5.8 months. These data support the suggestion of additive antitumor activity between gemcitabine and trastuzumab. Moreover, the combination of trastuzumab plus gemcitabine was well tolerated, with no cases of congestive heart failure [24].

**Trastuzumab Plus Capecitabine**

Early experiments investigating the combination of trastuzumab with 5-fluorouracil found that this combination was less effective than either drug alone, suggesting an antagonism in vitro [25]. However, further studies indicated that trastuzumab and the 5-fluorouracil prodrug capecitabine had at least additive antitumor activity in human breast cancer models [26], and this has been supported by recent studies in the clinical setting. In a multicenter phase II study of weekly trastuzumab with capecitabine (1,250 mg/m² twice a day [bid] on days 1–14, 3-weekly) in patients with pretreated MBC (n = 27), the objective response rate was 60% (four complete responses, eight partial responses; n = 20), median progression-free survival time was 28 weeks, and median overall survival time was 90 weeks [27]. This high response rate was mirrored in a phase II study of first-line trastuzumab–capecitabine therapy (capecitabine, 1,250 mg/m² bid on days 1–14, 3-weekly), in which an objective response rate of 76% (five complete responses, 14 partial responses; n = 19) was recorded [28]. In both phase II studies, the combination of trastuzumab plus capecitabine was generally well tolerated. There was no evidence of greater cardiotoxicity with this combination.

As recent studies have shown a survival benefit for trastuzumab plus docetaxel [11], and also for docetaxel plus capecitabine [29], there is a clear rationale for exploring the combination of trastuzumab plus docetaxel and capecitabine. A randomized trial of trastuzumab plus docetaxel with or without capecitabine in patients with HER-2-positive metastatic or locally advanced breast cancer (Capectibine, Herceptin, and Taxotere [CHAT]) is currently in progress. An interim safety analysis of CHAT (n = 110) reported a congestive heart failure incidence of 2% [30], which is the same as that reported in recent trials of trastuzumab plus docetaxel [11]. The rate of complicated neutropenia (26%) was also comparable with that seen in previous trials of trastuzumab–docetaxel or docetaxel–capecitabine combination therapy [11, 29]. As of November 2005, recruitment to CHAT was complete, with 225 patients enrolled, and efficacy results are awaited.

**Triple-Combination Regimens**

CHAT is not the only study to investigate trastuzumab as part of a triple-combination regimen. Several studies have shown that triple combinations are effective and produce high response rates (Table 1) [31–37]. For example, in a large randomized trial of first-line trastuzumab plus paclitaxel with or without carboplatin in patients with HER-2-positive MBC (n = 196), patients who received the triple combination had better outcomes than those who received trastuzumab and paclitaxel only (objective response rate, 52% vs. 36%; median TTP, 10.7 vs. 7.0 months; median survival, 36 vs. 32 months, respectively) [33]. Studies have shown that triple combinations of chemotherapeutic agents are generally feasible if overlapping toxicity profiles are avoided.

**Trastuzumab–Anthracycline Combinations**

Anthracyclines are a mainstay of therapy for patients with MBC; therefore, combination with trastuzumab is an area of active investigation. The significant benefit of adding trastuzumab to an anthracycline (mainly doxorubicin) and cyclophosphamide was clearly demonstrated in the pivotal trastuzumab combination trial (H0648g) [9, 13], despite a higher rate of cardiac events with this combination [12]. For this reason, several studies are examining the cardiac safety of trastuzumab combined with anthracyclines less cardiotoxic than doxorubicin, such as epirubicin or liposomal formulations of doxorubicin.

Initial analyses of the Herceptin, Cyclophosphamide, and Epirubicin (HERCULES) trial, a multicenter phase I–II trial of trastuzumab plus epirubicin–cyclophosphamide (EC) versus EC alone as first-line therapy for MBC, indicate that, because of its lower potential for cardiotoxic events compared with an anthracycline–cyclophosphamide
combination, it is feasible to combine trastuzumab with EC [38]. In phase I of this trial, patients with HER-2-positive disease initially received trastuzumab plus 60 mg/m² epirubicin (EC60; n = 26). Once it was established that this regimen was not associated with any dose-limiting toxicity, phase II of the trial was initiated. Patients with HER-2-positive disease were then enrolled into an arm of trastuzumab plus 90 mg/m² epirubicin (EC90; n = 25) and HER-2-negative patients received EC90 alone (n = 24). Both trastuzumab-containing arms met the criteria for acceptable tolerability, with only three patients experiencing a cardiac event: asymptomatic decline in LVEF to <50% in one patient receiving trastuzumab plus EC60 and congestive heart failure in two patients receiving trastuzumab plus EC90. One patient in the EC90-alone arm experienced arrhythmia/tachycardia. Response rates were 62% for trastuzumab plus EC60 and 64% for trastuzumab plus EC90. This compared favorably with a response rate of 26% in patients with HER-2-negative disease treated with EC90 alone [38].

In the M77035 trial, the efficacy and safety of combining trastuzumab with the liposomal doxorubicin TLC D-99 (Myocet®, Elan Pharmaceuticals, Princeton, NJ) was investigated [39]. By formulating doxorubicin within a liposome, exposure of normal cells to the cytotoxic agent is minimized, resulting in fewer cardiac events. The triple combination of trastuzumab plus paclitaxel (80 mg/m², weekly) plus TLC D-99 (50 mg/m², 3-weekly) was generally well tolerated. Two cases of cardiac insufficiency were reported but were not related to study treatment. The combination was also highly active, as evidenced by an objective response rate of 93% in 54 evaluable patients [39].

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>n</th>
<th>ORR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yardley et al. [36]</td>
<td>Carboplatin/paclitaxel</td>
<td>61</td>
<td>66</td>
</tr>
<tr>
<td>Perez et al. [32]</td>
<td>Carboplatin/paclitaxel weekly</td>
<td>48</td>
<td>81</td>
</tr>
<tr>
<td>Robert et al. [33]</td>
<td>Carboplatin/paclitaxel 3-weekly</td>
<td>43</td>
<td>65</td>
</tr>
<tr>
<td>Pegram et al. [31]</td>
<td>Carboplatin/paclitaxel</td>
<td>93</td>
<td>52</td>
</tr>
<tr>
<td>Pegram et al. [31]</td>
<td>Paclitaxel</td>
<td>95</td>
<td>36</td>
</tr>
<tr>
<td>Venturini et al. [37]</td>
<td>Epirubicin/docetaxel</td>
<td>62</td>
<td>79</td>
</tr>
<tr>
<td>Miller et al. [34]</td>
<td>Cisplatin/docetaxel</td>
<td>59</td>
<td>58</td>
</tr>
<tr>
<td>Yardley et al. [35]</td>
<td>Vinorelbine/docetaxel</td>
<td>45</td>
<td>67</td>
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<tr>
<td></td>
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<td>45</td>
<td>62</td>
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<tr>
<td>Abbreviation: ORR, objective response rate.</td>
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Trastuzumab in Combination with Hormonal Therapy

In estrogen receptor (ER)-positive patient populations, the rate of HER-2 positivity is 11%–35% [40–42]. In the trastuzumab pivotal trials, approximately 50% of patients with HER-2-positive metastatic disease were also ER positive [43]. Together, these data show that ER/HER-2-copositive disease is common, and it is of interest to explore specific treatment options for these patients. In the pivotal trials, hormone-receptor status did not affect the efficacy of trastuzumab given as a single agent or combined with chemotherapy [8–11, 44], indicating that trastuzumab is equally effective in ER-negative and ER-positive disease (Fig. 2).

Resistance to hormonal therapy, particularly tamoxifen, appears to be a characteristic of ER-positive, HER-2-positive tumors [45], and it has been hypothesized that the addition of trastuzumab to hormonal therapy may overcome
Trastuzumab in HER-2+ Metastatic Breast Cancer

The potential benefit of continuing trastuzumab treatment beyond disease progression with a new chemotherapy partner is a topic of considerable interest in clinical practice. To date, no results from randomized trials have been published; however, preclinical observations and a range of clinical data provide some evidence to support the concept of treatment beyond progression.

In preclinical studies using HER-2-positive human xenograft models, tumor regrowth was observed if levels of trastuzumab monotherapy were not sustained [49]. Also, continuous administration of trastuzumab in combination with a taxane after progression on trastuzumab monotherapy was shown to potentiate the antitumor activity of taxanes even after trastuzumab monotherapy was no longer effective (Fig. 3) [50].

Clinical evidence for trastuzumab treatment beyond progression was provided by the H0659g trial, an extension of the pivotal phase III H0648g trial, in which patients were given the opportunity to continue trastuzumab at the time of disease progression, either alone at a higher dose or with a new chemotherapy partner. Prolonged use of trastuzumab was safe and well tolerated and did not appear to increase the risk of cardiac dysfunction. The efficacy of trastuzumab treatment beyond progression was also encouraging, with an objective response rate of 11% and median RD of 6.7 months [51].

Follow-up of patients who progressed on trastuzumab plus docetaxel in a phase II MBC trial reported a median postprogression survival time of 20 months for six patients who continued trastuzumab treatment beyond progression [52], and results from several retrospective analyses of case series also indicate that patients continue to derive benefit from trastuzumab after disease progression [53–55]. In a retrospective analysis of patients with HER-2–positive MBC, objective response rates and TTP were maintained in patients receiving two or more trastuzumab-based regimens (Table 2) [53].

One large randomized trial investigating trastuzumab treatment beyond progression is currently under way: MO17038, a phase III study of trastuzumab plus capecitabine compared with capecitabine alone in women with HER-2–positive MBC progressing after trastuzumab in combination with a taxane or other chemotherapy.

Retreatment with Trastuzumab After Relapse Following (Neo)adjuvant Trastuzumab

Results from four large-scale global trials have demonstrated that adjuvant trastuzumab reduces the risk of disease recurrence by approximately 50% [56–58]. Further to this, the joint analysis of two of these trials demonstrated a signif-

**Table 2. Response rates and time to progression in metastatic breast cancer patients who received one, two, or more than two trastuzumab-based regimens [53]**

<table>
<thead>
<tr>
<th>Trastuzumab treatment</th>
<th>Objective response (%)</th>
<th>TTP (95% CI), mos</th>
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<tbody>
<tr>
<td>First (n = 54)</td>
<td>42.6</td>
<td>6 (5.40–6.60)</td>
</tr>
<tr>
<td>Second (n = 54)</td>
<td>25.9</td>
<td>6 (5.36–6.64)</td>
</tr>
<tr>
<td>Beyond second (n = 33)</td>
<td>30</td>
<td>6 (5.32–6.68)</td>
</tr>
</tbody>
</table>

Abbreviations: TTP, time to progression; CI, confidence interval.

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Figure 3. Addition of trastuzumab to paclitaxel in the human breast cancer xenograft model KPL-4 progressing on trastuzumab monotherapy [50].
icant survival benefit when patients received a total of 1 year of trastuzumab [57]. Based on these groundbreaking results, the use of trastuzumab in the adjuvant setting is becoming standard clinical practice. There is, therefore, a need to determine the optimal treatment regimen for those patients who relapse after adjuvant trastuzumab. The Retreatment after HERceptin Adjuvant (RHEA) retreatment trial is a phase II study of trastuzumab with or without a taxane for the first-line treatment of HER-2-positive MBC in women who have relapsed after (neo)adjuvant treatment with trastuzumab. It is anticipated that data from that trial will provide guidance on how best to treat this important subgroup of patients.

**CONCLUSIONS**

The combination of trastuzumab with chemotherapy is now standard for the first-line treatment of women with HER-2-positive MBC. The use of trastuzumab in the metastatic setting has changed HER-2-positive status from a marker of poor prognosis to one of better overall outcome. In a phase II trial of vinorelbine with or without trastuzumab according to HER-2 expression, women with HER-2-positive disease treated with vinorelbine plus trastuzumab had a better prognosis than patients with HER-2-negative disease treated with vinorelbine alone, thus suggesting that trastuzumab can change the natural history of HER-2–positive disease [22].

Novel trastuzumab-containing combinations with additive or even synergistic effects are of great interest, and several are being studied in ongoing clinical trials. Trastuzumab combined with cytotoxic agents such as taxanes, vinorelbine, gemcitabine, and capecitabine has been shown to produce superior response rates, TTP, and overall survival times in patients with MBC, and triplet combinations have the potential to offer additional benefit. Moreover, trastuzumab can be combined with a wide range of chemotherapy regimens while adding little to the toxicity profile of chemotherapy. Cardiac events can occur during trastuzumab treatment but are generally reversible and manageable. However, combinations with anthracyclines are not recommended outside clinical trials and combinations with less cardiotoxic anthracyclines are currently under investigation.

HER-2/ER-copositive disease is common: up to 25% of ER-positive tumors are also HER-2 positive. In this population, the combination of trastuzumab with hormonal therapies such as tamoxifen, exemestane, anastrozole, and letrozole is under investigation, and the results from several large clinical trials are eagerly anticipated. Trials of trastuzumab treatment beyond disease progression and retreatment after (neo)adjuvant relapse are also under way, and it is hoped that data from these trials will provide further guidance for clinical practice.

The number of trastuzumab-based treatment options in clinical practice is steadily increasing with each new clinical trial. Trastuzumab has become the foundation of care in HER-2-positive disease, and ongoing studies seek to provide further improvements in outcomes, broaden potential treatment approaches, and provide further information about the optimal use in clinical practice.

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**DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST**

C.J. has acted as a consultant and performed contract work for Roche within the past 2 years.

**REFERENCES**

Trastuzumab in HER-2+ Metastatic Breast Cancer


30 Wardley A, Antón-Torres A, Otero Reyes D et al. CHAT - an open-label, randomised, Phase II study of trastuzumab plus docetaxel with or without capecitabine in patients with advanced and/or metastatic HER2-positive breast cancer: second interim safety analysis, Poster 6094 presented at the 28th Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 8–11, 2005.


40 Arpino G, Green SJ, Allred DC et al. HER-2 amplification, HER-1 amplification (GA) [fluorescent in-situ hybridization (FISH)], and...
response rate (RR) for weekly (W) trastuzumab (H) and paclitaxel (T) in metastatic breast cancer (MBC) patients (pts). Proc Am Soc Clin Oncol 2002;21:56a.


