Safety and efficacy of the combination of trastuzumab with docetaxel for HER2-positive women with advanced breast cancer: A review of the existing clinical trials and results of the expanded access programme in the UK

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SUMMARY

Trastuzumab is a humanised monoclonal antibody against the extracellular domain of HER2 (human epidermal growth factor receptor-2) that is overexpressed in about 25% of human breast cancers. It has shown clinical benefit in HER2-positive breast cancer cases when used alone or in combination with chemotherapy. Trastuzumab increases the response rate to chemotherapy and prolongs survival when used in combination with taxanes. In this article, we review the clinical trials where trastuzumab has been administered together with docetaxel, and we present the results of the trastuzumab expanded access programme (EAP) in the UK. Combination of trastuzumab with docetaxel results in similar response rates and time-to-progression with the trastuzumab/paclitaxel combinations. The toxicity of the combination and the risk of heart failure are low. The clinical data for the docetaxel/trastuzumab combination indicate a favourable profile from both the efficacy and safety point of view and confirm the feasibility and safety of trastuzumab administration both as monotherapy and in combination with docetaxel.

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INTRODUCTION

HER2 (human epidermal growth factor receptor-2) is a transmembrane protein overexpressed in approximately 25% of breast cancers (1). HER2 overexpression leads to a poorer prognosis, both in terms of time-to-progression (TTP) and overall survival (OS). Trastuzumab (Herceptin®) is a humanised murine antibody which targets the extracellular domain of HER2. Pre-clinical studies have evaluated the activity of trastuzumab (or the equivalent mouse antibody, 4D5) against HER2-overexpressing breast cancer cell lines in vitro (2) and in vivo (3).

The first phase II clinical trials using trastuzumab as monotherapy reported response rates (RR) of 11.6% [46 patients (4)] to 15% [222 patients (5)] with median duration of response of 9.1 months and median survival of 13 months. The larger study incorporated patients with HER2 overexpression at the level of 2+ and 3+ by immunohistochemistry (IHC); a retrospective analysis restricted to patients whose tumours expressed HER2 of the 3+ level revealed a RR of 18% and a median survival of 16.4 months. Nine patients, all anthracycline-pre-treated, experienced cardiotoxicity demonstrated by a reduction in ejection fraction. These two trials led to the approval of trastuzumab as a second-line treatment for metastatic breast cancer (MBC). Further studies confirmed the efficacy of single agent trastuzumab in the first-line setting (6), with a RR of 34% in patients with HER2 amplification estimated by FISH.

TRASTUZUMAB/CHEMOTHERAPY COMBINATIONS: PRE-CLINICAL DATA

Pre-clinical studies have shown synergistic activity of trastuzumab in combination with various chemotherapeutic drugs, particularly the DNA-damaging agent cisplatin (7). It was subsequently found that the antibody interferes with the DNA-repair mechanisms (8). In vitro trastuzumab enhances the cytotoxic activity of many chemotherapeutic agents, including anthracyclines, taxanes, vinca alkaloids and epipodophyllotoxins (9). Interestingly, two studies suggested that trastuzumab showed true synergy in combination with docetaxel [CI = 0.61 (An index of 0.9–1.1 suggests additive effect, <1.1 synergistic and >1.1 antagonistic subadditive effect), p = 0.003 (10) and CI = 0.41, p = 0.001 (11)] with platinum. The trastuzumab/docetaxel combination resulted only in additive effect (CI = 0.91, p = 0.21). However, this was not confirmed in a recent in vitro study, where both paclitaxel and docetaxel exhibited an additive effect when combined with trastuzumab (CI 0.93 and 0.90, respectively) in the HER2-overexpressing cell line SK-Br3 (12). Both drugs were extremely synergistic with trastuzumab in the MCF-7 cell line (normal HER2 expression), and paclitaxel only exhibited synergy in the MDA-MB453 cell line (moderately high HER2 expression).

Finally, trastuzumab enhanced the anti-tumour activity of paclitaxel and doxorubicin in vivo in human breast cancer xenografts (13).

TRASTUZUMAB/CHEMOTHERAPY COMBINATIONS: CLINICAL DATA

The synergy of the trastuzumab-cisplatin combination was suggested in a phase II trial (14), though cisplatin is not usually considered to be one of the active agents for the treatment of MBC.

Trastuzumab is active in combination with paclitaxel, as was shown in a phase II clinical trial evaluating 88 patients where a RR of 62.4% was observed (15). A large phase III study randomised 469 patients to receive chemotherapy alone [either paclitaxol or doxorubicin/cyclophosphamide (AC) in patients who had not received anthracycline in the adjuvant setting] or in combination with trastuzumab (16). Patients who received trastuzumab had a significantly higher RR (50 vs. 32%, p < 0.001), longer TTP (7.4 vs. 4.6 months; p < 0.001) and longer survival (25.1 vs. 20.3 months; p = 0.01), despite the crossover of 66% of the patients from the chemotherapy alone to the trastuzumab/chemotherapy or trastuzumab alone arm, on disease progression. Due to the high cardiotoxicity rate in the trastuzumab/AC arm, only the paclitaxel/trastuzumab combination was approved by the FDA for the use as first-line treatment in HER2-overexpressing MBC.

A phase III trial comparing trastuzumab/paclitaxel vs. trastuzumab/paclitaxel/carboplatin as first-line treatment in women with MBC showed a better RR for the triplet (52 vs. 36%, p = 0.04) with a better TTP (11.2 vs. 6.9 months, p = 0.007); however, there was no statistically significant difference in overall survival (92 vs. 87 months, p = 0.2) (17). Two phase II studies evaluating the combination of trastuzumab with docetaxel and either cisplatin (18) or carboplatin (19) have demonstrated RRs of 79% (cisplatin, 62 patients) and 56% (carboplatin, 62 patients). These regimens are now the subject of phase III studies.

A small study addressed the efficacy and safety of the combination of trastuzumab with vinorelbine in 40 patients with HER2 positive (2+ or 3+ in IHC). The combination was highly active with a RR of 75% (80% in HER2 3+ overexpressors) (20). Similar results were obtained in another study, again enrolling 40 patients (21). A similar study presented last year at the San Antonio meeting resulted in a rate of 70% objective response in 37 evaluable patients (22). Several other studies are underway evaluating the trastuzumab/vinorelbine combination (23).

DOCETAXEL/TRASTUZUMAB COMBINATIONS

Docetaxel is an effective agent in the treatment of MBC (24). It has been approved for the first- and second-line treatment
of MBC and has been tested in the adjuvant setting. There is also evidence from in vitro data suggesting a synergistic effect in combination with trastuzumab (10) and some clinical data suggesting that HER2 overexpressing tumours may respond better to taxanes (25).

A phase II trial was designed to examine the efficacy and safety of the trastuzumab and docetaxel combination in 25 women with HER2-positive MBC, and the final results were recently reported (26,27). Most of the patients had received prior chemotherapy in the adjuvant/neoadjuvant setting, and nine had received first-line chemotherapy for metastatic disease. RR was 67% (7 CR and 21 PR in 42 evaluable patients) and 72% in the HER2 3+ patients (n = 32). Median progression-free survival was 9 months, time to treatment failure (TTF) 8 months and duration of response 12 months. Symptomatic cardiotoxicity (grade 3) was observed in one patient and three more had an asymptomatic decrease in left ventricular ejection fraction (LVEF). The main toxicity of the regimen was neutropenia. Other trials have reported similar rates of objective response. Table 1 summarises the results of the phase II clinical trials for the trastuzumab and docetaxel combination in women with MBC [Other trials: (28–34)].

### M77998 STUDY REPORT: EXPANDED ACCESS PROGRAMME IN UK

**Patients/methods**

Expanded access programme (EAP) was initiated in 1999 and was a non-randomised open-label study conducted in 32 centres throughout UK to assess the safety of trastuzumab in HER2-positive MBC patients, alone or in combination with a taxane. The treatment arms and recruitment are summarised in Table 2. The trial mainly included patients in the first/second-line of treatment for the trastuzumab plus taxane combination and in the second/third-line treatment for the trastuzumab monotherapy. Eligible patients were between 18 and 75 years old (>75 could be included by investigators discretion) women with MBC and HER2 overexpression at the level of +2/+3 by IHC. Pregnant, lactating or women on childbearing potential with inadequate contraception were excluded from the trial as well as patients with clinically significant cardiac disease, prior treatment with doxorubicin at a cumulative dose over 300 mg/m² or epirubicin >750 mg/m². Prior taxane treatment was allowed only in the trastuzumab monotherapy arm. For the trial, trastuzumab was provided by Roche Products Limited, and Aventis UK offered a discount on the docetaxel. Finally, only four patients were recruited in the trastuzumab plus paclitaxel arm, mainly due to logistics.

Trastuzumab was given in the recommended manner by IV infusion with a loading dose of 4 mg/kg followed by weekly administration of 2 mg/kg until disease progression.

The majority of patients entered into the study had a performance status (ECOG) of either 0 or 1 (41 and 42.9%, respectively). Sixteen per cent of subjects overall had an ECOG score of 2. The median number of days since diagnosis of breast cancer was 35.8 months (ranging from 13 days to 23.6 years).

As the primary objective of the trial was safety, results from survival or TTF could not be obtained. However, because time-on-treatment data are available, they were used as a surrogate marker for TTF. Time-on-treatment was computed

### Table 1 Phase II clinical trials of trastuzumab and docetaxel in metastatic breast cancer

| Trial                | Reference | Docetaxel schedule | n  | PR (%) |
|----------------------|-----------|--------------------|----|--------|
| Kuzur et al. 2000    | (32)      | 75 mg/m² q3-w      | 16 | 44     |
| Malik et al. 2000    | (31)      | 33 mg/m² weekly    | 6  | 83     |
| Nicholson et al. 2000| (34)      | 35 mg/m² weekly    | 33 | 54     |
| Uber et al. 2001     | (33)      | 35 mg/m² weekly    | 19 | 63     |
| Meden et al. 2001    | (30)      | 35 mg/m² weekly    | 12 | 50     |
| Esteva et al. 2002   | (28)      | 35 mg/m² weekly (3/4 weeks, 1/4 week rest) | 30 | 63     |
| Raab et al. 2002     | (29)      | 100 mg/m² 3-q-w or 35 mg/m² weekly | 25 | 63     |
| Montemurro et al. 2003| (27)     | 75 mg/m² q3-w     | 23 | 70     |

Herceptin® was administered as a 4 mg/kg initial dose followed by 2 mg/kg weekly until progression. In the study by Esteva et al., Herceptin was administered every week for 3/4 weeks with 1 week rest.

### Table 2 Expanded access programme, treatment arms and numbers of recruited patients

| Treatment arm | Trastuzumab schedule | Taxane schedule | n   | First | Second | Third | Fourth |
|---------------|----------------------|-----------------|-----|-------|--------|-------|--------|
| Trastuzumab alone | 4 mg/kg followed by 2 mg/kg weekly* | –               | 75  | 2     | 42     | 31    |
| Trastuzumab plus docetaxel | 4 mg/kg followed by 2 mg/kg weekly* | 100 mg/m², 3-weekly, for six cycles | 87  | 42    | 34     | 10    | 1      |
| Trastuzumab plus paclitaxel | 4 mg/kg followed by 2 mg/kg weekly* | 175 mg/m², 3-weekly, for six cycles | 4   |       |        |       |        |

Trastuzumab continued until disease progression.

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from the first chemotherapy and estimated by the Kaplan-Meier method (35). Serious adverse events were reported from each centre. All patients had a pre-treatment assessment of the cardiac function. In some patients \(n = 56\), LVEF was estimated by MUGA scan.

**Results**

Few patients \(n = 4\) received paclitaxel with trastuzumab and were not included in the final analysis. Kaplan-Meyer curves for time-on-treatment are shown in Figure 1. The median time-on-treatment was 6 and 10 months for the trastuzumab alone and trastuzumab plus docetaxel arms, respectively. The difference, however, can be largely attributed to the fact that trastuzumab alone was used mainly as a second/third-line treatment whilst the combination as first/second-line (Table 2). In previous trials, trastuzumab as single-agent treatment resulted in a higher response ratio (RR) and OS when it was used as first-line (6) than when used as a second/third-line treatment (5) (at first-line RR = 35% and OS = 24.4 months vs. at second/third-line RR = 18% and OS = 16.4 months). At the cut-off for the current analysis, 12 patients from the trastuzumab alone group (16.0%) and 21 from the trastuzumab and docetaxel group (24.1%) were still on treatment.

Table 3 presents the results of the Cox’s proportional hazards analysis. The hazard ratios (95% CI) indicate that higher numbers of previous hormonal treatments and lower performance status were associated with shorter times on treatment. Higher albumin levels and longer initial disease-free survival were associated with longer time on treatment. After adjustment of all the other variables in the model including the line of treatment, the hazard of disease progression was lower, and thus prognosis was better for patients receiving docetaxel with trastuzumab compared to those who take trastuzumab alone [hazard ratio (95% CI) = 0.49 (0.311, 0.775)].

As regards cardiac adverse events, one patient in the trastuzumab alone arm developed supraventricular tachycardia and two patients in the combination arm had an episode of atrial fibrillation whilst on treatment. In 20 patients in the trastuzumab monotherapy arm and in 36 patients from the combination arm, LVEF was estimated by MUGA scan before treatment and in 3-month intervals. Figure 2 displays the results of the baseline MUGA scan and the lowest LVEF estimated. The average fall in LVEF was 4 and 7% in the monotherapy and the combination arms, respectively. In one patient in the trastuzumab monotherapy arm, LVEF levels fell by more than 15% to absolute LVEF levels lower than 50%. Five patients in the combination arm had a fall in LVEF by more than 15%, but only one to absolute LVEF levels lower than 50%. This patient developed symptomatic heart failure; trastuzumab/docetaxel was discontinued and LVEF returned to normal. Trastuzumab was re-introduced later, a partial response to the treatment was achieved and no fall in LVEF was observed.

**Summary**

Overall, the EAP resulted in comparable data with previous trials either for the docetaxel/trastuzumab combination (as compared to the paclitaxel/trastuzumab data by Slamon et al.) or for the trastuzumab alone arm (as compared with the data from Cobleigh et al.). The combination is relatively safe with the risk of cardiotoxicity at acceptable levels.

**Conclusion**

Trastuzumab is a new and effective treatment for patients with MBC that overexpress HER2 at the IHC 3+ level. It increases the RR to chemotherapy and prolongs survival when used as a first-line in combination with taxanes. Combination of trastuzumab with docetaxel results in similar RRs and survival benefits compared to single-agent therapy.
time-to-progression with the trastuzumab/paclitaxel combinations. The toxicity of the combination and the risk of heart failure are low. Asymptomatic decreases in LVEF are not uncommon but do not require specific treatment as long as LVEF remains over 50%.

Recently, the results of a European phase II randomised trial of trastuzumab plus docetaxel vs. docetaxel alone as first-line therapy in 186 patients with HER2-positive MBC were reported. The results showed a statistical significant difference in median survival (24.1 vs. 13.2 months, \( p = 0.0001 \)) in favour of the combination (36). The incidence of congestive heart failure was approximately 1% comparable to that reported of the paclitaxel plus trastuzumab combination.

Overall, the clinical data for the docetaxel/trastuzumab combination indicate a favourable profile from both the efficacy and the safety point of view. The EAP gave clinicians, experience in settings that more closely reflected normal clinical practice as compared with clinical trials. It confirmed the feasibility and safety of trastuzumab administration both as monotherapy and in combination with docetaxel.

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**Table 3** Results from the Cox’s proportional hazards model for time to disease progression (days): intention-to-treat population

| Treatment group:               | Hazard ratio | 95% confidence Interval | p value |
|-------------------------------|--------------|-------------------------|---------|
| Trastuzumab (baseline)        | 1.00         |                         |         |
| Trastuzumab and docetaxel     | 0.49         | 0.311–0.775             | 0.0023  |
| Performance status (ECOG)     |              |                         |         |
| 0 (baseline)                  | 1.00         |                         |         |
| 1                             | 1.51         | 0.980–2.322             | 0.0618  |
| 2                             | 2.60         | 1.367–4.965             | 0.0036  |
| Line of treatment*            | 0.72         | 0.443–1.171             | 0.185   |
| Age*                          | 1.01         | 0.989–1.025             | 0.458   |
| Time since diagnosis (months)*| 0.99         | 0.985–0.997             | 0.0047  |
| Number of prior:              |              |                         |         |
| Hormonal treatments*          | 1.23         | 0.999–1.519             | 0.0512  |
| Chemotherapy treatments*      | 1.13         | 0.760–1.674             | 0.5512  |
| Clinical laboratory tests:     |              |                         |         |
| Albumin*                      | 0.94         | 0.897–0.977             | 0.0026  |
| Haemoglobin*                  | 1.00         | 0.992–1.004             | 0.4932  |

*Estimated change in the hazard for each unit increase.

**Figure 2** Left ventricular ejection fraction (LVEF) estimated with MUGA scan in patients before treatment (baseline) and at the lowest LVEF after treatment.
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