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Recent advances in the treatment of metastatic breast cancer by adding trastuzumab

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Human epidermal growth factor receptor 2 (HER2) overexpression occurs in 15–20% of breast cancers and represents an aggressive form of the disease that does not respond well to chemotherapy. As such, HER2 overexpression is associated with a poor prognosis, with the median survival from first diagnosis being only 3 years, compared with a figure of 6–7 years for patients with normal levels of HER2-oncoprotein expression [1]. Single-agent trastuzumab is an effective therapy for the treatment of patients with HER2-positive disease, and studies have demonstrated response rates in the second-line setting of 6% and 18% in patients with HER2 2+ and 3+ disease (as assessed by fluorescence *in situ* hybridisation [FISH]), respectively. This figure was increased to 35% with first-line use. However, in order to achieve the best possible outcome for patients with metastatic breast cancer, targeted therapy must be optimised. One of the key ways that this can be achieved is through combination with cytotoxic agents. Indeed, a preclinical study conducted by Pegram and colleagues [2] reported on the outcomes of combination of trastuzumab with a number of cytotoxic agents. While the combination of trastuzumab with either doxorubicin, epirubicin, or paclitaxel had an additive effect, combination of trastuzumab with docetaxel was found to be synergistic (Fig. 1) [2].

This information, coupled with evidence demonstrating the effectiveness of docetaxel in the second-line setting, either as monotherapy [3–7] or as part of combination therapy [8] and also first line in combination with other agents [9,10], made docetaxel an attractive option for combination therapy with trastuzumab for use in patients with HER2-positive disease. Indeed, data from three phase II studies have reported response rates in the range of 44–70% when the docetaxel/trastuzumab combination is used first or second line in HER2-overexpressing metastatic breast cancer [11–13]. Although many of these studies were small in size, they all suggested that the response rate was

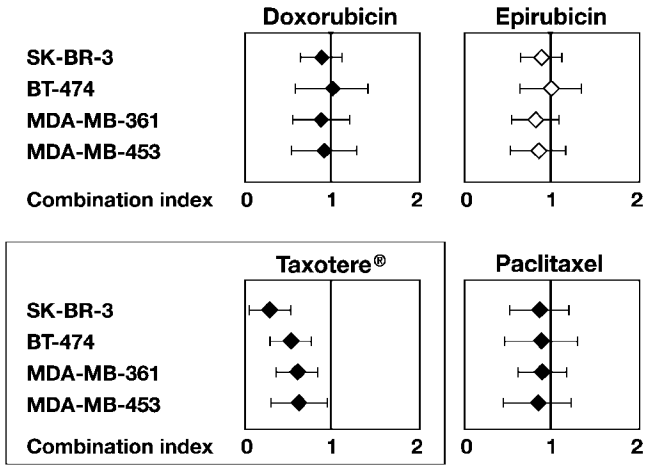

Fig. 1. *In vitro* synergism of docetaxel and trastuzumab.

increased for combination therapy compared with single-agent docetaxel.

Other agents that have been evaluated as part of combination therapy with trastuzumab include vinorelbine and paclitaxel. Combination therapy comprising trastuzumab (4 mg/kg at week 1, with 2 mg/kg at subsequent weeks) and vinorelbine (25 mg/m^2/week) as either first-, second- or third-line therapy was assessed in a phase II study of 40 women with advanced HER2-positive breast cancer. This combination demonstrated an objective response rate (ORR) of 75% [14]. Another study investigating the same regimen in patients who either had received no prior therapy or first-line therapy for metastatic disease reported an ORR of 61% [15]. Two phase II studies investigated similar combinations of trastuzumab with vinorelbine as first-line therapy. Jahanzeb and colleagues [16] reported an ORR of 78% with a vinorelbine dose of 30 mg/m^2, and Burnstein and colleagues [17] reported a 68% ORR for combination therapy, including weekly vinorelbine at a dose of 25 mg/m^2.

A phase II study that assessed the combination of trastuzumab (4 mg/kg at week 1, with 2 mg/kg at subsequent weeks) and paclitaxel (90 mg/m^2/week) in women with

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HER2-normal and HER2-overexpressing metastatic breast cancer who had received up to three prior chemotherapy regimens, including prior anthracycline and taxoid therapy, reported an ORR of 61% [18]. The seminal paper by Slamon and colleagues [19] was a four-armed study, in which two of the arms compared single-agent paclitaxel and combination therapy comprising paclitaxel and trastuzumab. In this study, 469 patients were randomly assigned to receive either standard chemotherapy alone ($n=234$) or standard chemotherapy plus trastuzumab ($n=235$) [19]. Patients who had not previously received adjuvant therapy with an anthracycline received doxorubicin (or, in the case of 36 women, epirubicin) and cyclophosphamide, with ($n=143$) or without ($n=138$) trastuzumab. Patients who had previously received adjuvant therapy with an anthracycline were treated with paclitaxel alone ($n=96$) or paclitaxel with trastuzumab ($n=92$). The primary endpoint for this study was time to progression (TTP), and secondary endpoints were ORR, duration of response, time to treatment failure (TTF) and overall survival (OS). Compared with single-agent paclitaxel, combination therapy produced a significant benefit in terms of ORR (17% versus 41%, respectively; $P<0.001$) and TTP (3.0 versus 6.9 months; $P<0.001$). However, OS was not significantly prolonged in patients who received trastuzumab and paclitaxel compared with patients who received paclitaxel alone, the survival periods being 22.1 months and 18.4 months, respectively. Incidence of cardiotoxicity was retrospectively analysed, showing a 13% incidence of symptomatic or asymptomatic cardiac dysfunction in the patient group who received combination therapy comprising paclitaxel and trastuzumab [19].

The efficacy and safety of first-line therapy comprising trastuzumab and docetaxel in patients with HER2-positive metastatic breast cancer were investigated in the M77001 study [20]. Patients were randomly assigned to receive six cycles of docetaxel 100 mg/m^2 every 3 weeks, with or without a loading dose of 4 mg/kg trastuzumab, followed by a weekly dose of 2 mg/kg until disease progression. Patients in the docetaxel monotherapy arm who progressed were allowed to cross over to receive trastuzumab at disease progression. The primary endpoint of this study was ORR, and secondary endpoints were safety, TTP, TTF, duration of response, 1-year survival and OS. This trial met all of its endpoints, with the trastuzumab/docetaxel combination producing a significant doubling of the ORR (61% compared with the 34% response achieved with single-agent docetaxel; $P=0.0002$). Seven per cent of patients experienced a complete response in the combination group, and the percentage of patients with stable disease was reduced from 44% with docetaxel alone to 27% with the combination, indicating that the course of disease could be altered with this therapy. The trial met all of its secondary endpoints, with the combination producing significant improvements in median duration of response, TTP, median TTF, and median OS, compared with docetaxel monotherapy (Table 1). Overall survival was increased from 22.7 months with single-agent docetaxel to 31.2 months with the combination – an impressive improvement of 8.5 months. The median duration of response was more than doubled, increasing from 5.7 to 11.7 months. Similarly, the TTP was significantly increased from 6.1 to 11.7 months, as was median TTF, which was increased from 5.3 to 9.8 months.

Table 1
Efficacy results of the M77001 trial

Outcome	Docetaxel alone ($n=94$)	Docetaxel + trastuzumab ($n=92$)	P-value
Median OS (months)	22.7	31.2	0.0325
Median DR[a] (months)	5.7	11.7	0.009
TTP (months)	6.1	11.7	0.0001
Median TTF (months)	5.3	9.8	0.0001

[a] DR: duration of response.

The combination therapy performed equally well in all subgroups, even in patients with previous exposure to anthracyclines and patients over the age of 50 years. The number of metastatic organ sites did not influence the outcome of chemotherapy, as both patients with up to two, and patients with more than two metastatic organ sites, who received combination therapy with trastuzumab and docetaxel, achieved better outcomes compared with those patients who received docetaxel monotherapy. Similarly, patients receiving the combination therapy had better outcomes than those who received docetaxel alone, independent of their hormone-receptor status or their Eastern Cooperative Oncology Group (ECOG) performance status. An additional retrospective analysis investigated the outcome of patients known to have crossed over to receive trastuzumab after progression on docetaxel monotherapy. The Kaplan–Meier plots of those patients receiving trastuzumab plus docetaxel upfront, versus those who received trastuzumab upon cross-over, show a clear trend suggesting that the greatest benefit is derived from upfront treatment with the combination (Fig. 2).

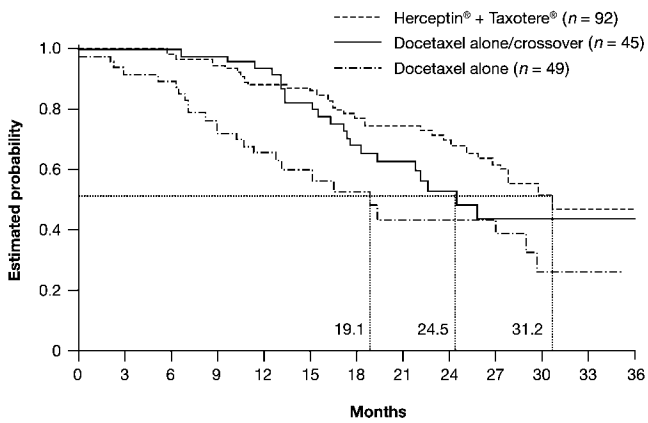

Fig. 2. M77001 overall survival (ITT analysis).

Table 2
Comparison of the response rates achieved from the combination of trastuzumab and different cytotoxic agents

Authors	Prior therapy	Cytotoxic agent/dose/schedule	ORR (%)
Burstein *et al.* [14]	First, second and third	Vinorelbine (25 mg/m^2/week)	75
Jahanzeb *et al.* [16]	First	Vinorelbine (30 mg/m^2/week)	78
Burstein *et al.* [17]	First	Vinorelbine (25 mg/m^2/week)	68
Slamon *et al.* [19]	After anthracycline	Paclitaxel (175 mg/m^2 q3w)	41
Seidman *et al.* [18]	First, second and third	Paclitaxel (90 mg/m^2/week)	57
Burris *et al.* [21]	First or second	Docetaxel (75 mg/m^2 q3w)	54
Marty *et al.* [20]	First	Docetaxel (75 mg/m^2 q3w)	61

Table 3
Cross-trial comparison of trastuzumab/taxoid combination therapy

Outcome	H0648g			M77001		
	Paclitaxel	Paclitaxel + trastuzumab	*P*-value	Docetaxel	Docetaxel + trastuzumab	*P*-value
ORR (%)	17.0	41.0	<0.001	34.0	61.0	0.0002
TTP (mo)	3.0	6.9	<0.001	6.1	11.7	0.0001
OS (mo)	18.4	22.1	0.17	22.7	31.2	0.0325

The incidence of non-haematological adverse events in the M77001 trial was similar in both arms. There were two cases of clinical congestive heart failure, both of which occurred in patients who had received the combination therapy and who had also received prior anthracycline therapy. One of these patients had a baseline left ventricular ejection fraction (LVEF) of 60%, and the other patient had progressed on previous trastuzumab therapy, having had no evidence of cardiac dysfunction during therapy, and had subsequently entered a trial of an investigational anthracycline. The incidence of leukopenia, neutropenia, and febrile neutropenia was slightly increased in the group who received combination therapy, compared with those who received docetaxel monotherapy, but this incidence was not significantly different. Although the rate of febrile neutropenia was greater for the docetaxel/trastuzumab combination than for docetaxel monotherapy (23% versus 17%), this value is only just above the National Comprehensive Cancer Network's recommended threshold of 20% for intervention with growth factors. As discussed earlier in this supplement, occurrence of neutropenia and febrile neutropenia in at-risk patients can be effectively managed by prophylactic granulocyte colony-stimulating growth factor (G-CSF) support.

In summary, a number of phase II trials have demonstrated response rates of up to 75% for combination therapy comprising trastuzumab and chemotherapy (Table 2).

Two pivotal studies [19,20] have also demonstrated efficacy advantages for trastuzumab/taxoid combination therapy over single-agent taxoid therapy. Comparison of the results from these two pivotal studies demonstrates that significant increases in ORR and TTP are produced by the combination of trastuzumab with either paclitaxel or docetaxel (Table 3). However, the increase in OS achieved with combination therapy, compared with single-agent taxoid therapy, was significant only for docetaxel and not for paclitaxel (Table 3). Differences in the patient populations of these two studies may have contributed to this, including an increased number of HER2 2+, FISH-negative patients in the paclitaxel study compared with the docetaxel study. Therefore, once the FISH-negative patients were excluded the evaluable population was smaller in the paclitaxel study, meaning that statistical significance was harder to achieve. In addition, the paclitaxel regimen used is now considered inferior compared with newer regimens and also, prior adjuvant anthracycline use with relapse within 2 years was an essential criterion for inclusion in the paclitaxel, but not the docetaxel study.

In conclusion, few trials show a survival advantage in the metastatic setting. The results of the M77001 trial demonstrate an impressive OS of 31.2 months, and a doubling of RR and TTP for docetaxel/trastuzumab combination therapy compared with docetaxel monotherapy. It is well known that the combination of trastuzumab with docetaxel is synergistic, whereas the combination of this agent with paclitaxel produces only additive results [2]. Indirect comparison of clinical trial data suggests that this advantage is translated to the clinical setting; therefore docetaxel is the taxoid of choice for combination with trastuzumab. Cardiotoxicity was not an issue for the docetaxel/trastuzumab combination, which further supports its use in the adjuvant setting as opposed to anthracycline-based combinations.

In addition to the synergistic interaction between trastuzumab and docetaxel, the Pegram study [2] also reported

synergistic interactions between trastuzumab and carboplatin. These findings formed the basis for the investigation of the TCH (docetaxel/carboplatin/trastuzumab) regimen, the aim of which was to maintain efficacy while reducing the potential for cardiotoxicity from co-administration of an anthracycline with trastuzumab, through substitution of the anthracycline component with carboplatin. The efficacy and safety of the TCH regimen in the metastatic setting is being investigated in the Breast Cancer International Research Group (BCIRG) 007 trial, in which 444 patients were randomised to receive treatment with either TH (eight cycles of docetaxel (100 mg/m^2) plus weekly trastuzumab during chemotherapy, then every 3 weeks until disease progression), or TCH (eight cycles of docetaxel 75 mg/m^2 + carboplatin 6AUC plus weekly trastuzumab during chemotherapy, then every 3 weeks until disease progression). Similarly, evaluation of the TCH and the AC–TH (anthracycline/cyclophosphamide followed by docetaxel/trastuzumab) regimens in the adjuvant setting is currently underway in the BCIRG 006 trial. Preliminary safety results from this trial were reported at the ECCO 13 meeting [22], and preliminary efficacy results were presented at the 2005 San Antonio Breast Cancer Conference, demonstrating a highly statistically significant DFS benefit for two docetaxel/trastuzumab-containing regimens after a short follow-up of 23 months. Compared with the AC–T control arm, the AC–TH regimen was associated with a 51% reduction in the risk of relapse (HR = 0.49; $P = 0.00000048$) and the TCH regimen was associated with a 39% reduction in risk of relapse (HR = 0.61; $P = 0.00015$) [23]. The results of this and other studies (the discussion of which is outside the scope of this article) that have evaluated the effect of trastuzumab/taxoid combinations [24,25], will confirm the place of such therapies in the treatment of patients with HER2-positive, early-stage breast cancer.

References

1. Slamon DJ, Clark GM, Wong SG, *et al.* Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 1987, **235**(4785), 177–82.
2. Pegram MD, Konecny GE, O'Callaghan C, Beryt M, Pietras R, Slamon DJ. Rational combinations of trastuzumab with chemotherapeutic drugs used in the treatment of breast cancer. *J Natl Cancer Inst* 2004, **96**(10), 739–49.
3. Chan S, Friedrichs K, Noel D, *et al.* Prospective randomized trial of docetaxel versus doxorubicin in patients with metastatic breast cancer. *J Clin Oncol* 1999, **17**(8), 2341–54.
4. Nabholtz JM, Senn HJ, Bezwoda WR, *et al.* Prospective randomized trial of docetaxel versus mitomycin plus vinblastine in patients with metastatic breast cancer progressing despite previous anthracycline-containing chemotherapy. 304 Study Group. *J Clin Oncol* 1999, **17**(5), 1413–24.
5. Sjöstrom J, Blomqvist C, Mouridsen H, *et al.* Docetaxel compared with sequential methotrexate and 5-fluorouracil in patients with advanced breast cancer after anthracycline failure: a randomised phase III study with crossover on progression by the Scandinavian Breast Group. *Eur J Cancer* 1999, **35**(8), 1194–201.
6. Bonneterre J, Roche H, Monnier A, *et al.* Docetaxel vs 5-fluorouracil plus vinorelbine in metastatic breast cancer after anthracycline therapy failure. *Br J Cancer* 2002, **87**(11), 1210–5.
7. Jones SE, Erban J, Overmoyer B, *et al.* Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer. *J Clin Oncol* 2005, **23**(24), 5542–51.
8. O'Shaughnessy J, Miles D, Vukelja S, *et al.* Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. *J Clin Oncol* 2002, **20**(12), 2812–23.
9. Nabholtz JM, Falkson C, Campos D, *et al.* Docetaxel and doxorubicin compared with doxorubicin and cyclophosphamide as first-line chemotherapy for metastatic breast cancer: results of a randomized, multicenter, phase III trial. *J Clin Oncol* 2003, **21**(6), 968–75.
10. Bontenbal M, Creemers GJ, Braun HJ, *et al.* Phase II to III study comparing doxorubicin and docetaxel with fluorouracil, doxorubicin, and cyclophosphamide as first-line chemotherapy in patients with metastatic breast cancer: results of a Dutch Community Setting Trial for the Clinical Trial Group of the Comprehensive Cancer Centre. *J Clin Oncol* 2005, **23**(28), 7081–8.
11. Montemurro F, Choa G, Faggiuolo R, *et al.* A phase II study of three-weekly docetaxel and weekly trastuzumab in HER2-overexpressing advanced breast cancer. *Oncology* 2004, **66**(1), 38–45.
12. Meden H, Beneke A, Hesse T, Novophashenny I, Wischnewsky M. Weekly intravenous recombinant humanized anti-P185HER2 monoclonal antibody (herceptin) plus docetaxel in patients with metastatic breast cancer: a pilot study. *Anticancer Res* 2001, **21**(2B), 1301–5.
13. Esteva FJ, Valero V, Booser D, *et al.* Phase II study of weekly docetaxel and trastuzumab for patients with HER-2-overexpressing metastatic breast cancer. *J Clin Oncol* 2002, **20**(7), 1800–8.
14. Burstein HJ, Kuter I, Campos SM, *et al.* Clinical activity of trastuzumab and vinorelbine in women with HER2-overexpressing metastatic breast cancer. *J Clin Oncol* 2001, **19**(10), 2722–30.
15. Bayo J, Sanchez-Rovira P, Perez-Carrion R, *et al.* Trastuzumab and vinorelbine combination in the treatment of Her2 positive metastatic breast cancer. *Proc ASCO* (Post-meeting edition) 2004, **22**(14S), Abstr. 673.
16. Jahanzeb M, Mortimer JE, Yunus F, *et al.* Phase II trial of weekly vinorelbine and trastuzumab as first-line therapy in patients with HER2(+) metastatic breast cancer. *Oncologist* 2002, **7**(5), 410–7.
17. Burstein HJ, Marcom P, Lambert-Falls R, *et al.* Multicenter phase II study of trastuzumab (herceptin; H) and vinorelbine (navelbine; N) as first-line therapy for HER2 overexpressing metastatic breast cancer (HER2+ MBC). *Proc ASCO* 2002, **21**, 211. Abstract.
18. Seidman AD, Fornier MN, Esteva FJ, *et al.* Weekly trastuzumab and paclitaxel therapy for metastatic breast cancer with analysis of efficacy by HER2 immunophenotype and gene amplification. *J Clin Oncol* 2001, **19**(10), 2587–95.
19. Slamon DJ, Leyland-Jones B, Shak S, *et al.* Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001, **344**(11), 783–92.
20. Marty M, Cognetti F, Maraninchi D, *et al.* Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. *J Clin Oncol* 2005, **23**(19), 4265–74.
21. Burris 3rd, HA. Docetaxel (Taxotere) in HER-2-positive patients and in combination with trastuzumab (Herceptin). *Semin Oncol* 2000, **27**(2 Suppl 3), 19–23.
22. Slamon D, Robert N, Pienkowski T, *et al.* BCIRG 006: Superior cardiac safety of adjuvant docetaxel (T), carboplatin (C) and trastuzumab (H) compared to doxorubicin (A) and cyclophosphamide (Cyc) followed by TH in patients with early stage breast cancer and altered HER2 gene. *Eur J Cancer Suppl* 2005, **3**(2), 74.
23. Slamon D, Robert N, Pienkowski T, *et al.* Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxel (ACT) with doxorubicin and cyclophosphamide followed by docetaxel

and trastuzumab (ACTH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2 positive early breast cancer patients: BCIRG 006 study. In: *SABCS 2005*; 2005, Abstr. 1.

24. Romond EH, Bryant J, Suman V, *et al.* Combined analysis of NSABP-B31/NCCTG-N9831. *Proc ASCO 2005*, Oral presentation.

25. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, *et al.* Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 2005, **353**(16), 1659–72.