Trastuzumab in Combination with Chemotherapy in Metastatic Disease

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A variety of chemotherapeutic agents and regimens have been studied in combination with the humanized monoclonal antibody trastuzumab for the treatment of patients with HER2-positive metastatic disease. The most recent related major study evaluated the combination of docetaxel and trastuzumab, and as with prior similar trials, progression-free and overall survival advantages were observed with the addition of trastuzumab. Additional studies have attempted to define whether continuation of trastuzumab beyond progression is safe and efficacious. While no definitive efficacy data exist, Dr Debu Tripathy demonstrated that this strategy results in disease response without significant excess toxicity compared to chemotherapy alone.

PHASE III STUDY COMPARING TRASTUZUMAB AND PACLITAXEL WITH AND WITHOUT CARBOPLATIN IN PATIENTS WITH HER2-POSITIVE METASTATIC BREAST CANCER

Parameters	TPC regimen	TP regimen	*p*-value
Response rate (RR)	52% (n=89)	36% (n=94)	0.04
Overall response in HER2 IHC 3+	57%	37%	0.03
Time to progression (TTP)	10.7 months	7.0 months	0.016
TTP in HER2 IHC 3+	14.0 months	7.1 months	0.007
Overall Survival (OS)	36 months	32 months	0.496
OS in HER2 IHC 3+	42 months	29 months	0.29

TPC = trastuzumab, paclitaxel, carboplatin; TP = trastuzumab, paclitaxel

"Overall response (OR) and time to progression (TTP) were significantly improved with TPC compared to TP... . Therapy was well-tolerated on both arms of the study. Grade 3-4 neutropenia and thrombocytopenia were more common with TPC, as expected. There was no difference in fever/neutropenia, neuropathy, fatigue, and other toxicities between study arms. There were 2 cases of congestive heart failure, seen in the TP arm."

SOURCE: Robert N et al. **Randomized Phase III study of trastuzumab, paclitaxel, and carboplatin versus trastuzumab and paclitaxel in women with HER-2 overexpressing metastatic breast cancer: An update including survival.** Presentation. ASCO, 2004.

PHASE II RANDOMIZED TRIAL OF DOCETAXEL WITH OR WITHOUT TRASTUZUMAB AS FIRST-LINE THERAPY IN WOMEN (N=188) WITH HER2-POSITIVE METASTATIC BREAST CANCER

	Docetaxel + trastuzumab	Docetaxel alone*	*p*-value
Overall response rate	61%	36%	0.001
Median survival	27.7 months	18.3 months	Not reported
Median time to progression	10.6 months	6.1 months	0.0001
Median duration of response	8.3 months	4.2 months	Not reported
Febrile neutropenia	23%	17%	Not reported

* 44 percent of the patients treated with docetaxel alone crossed over to receive trastuzumab

SOURCE: Extra JM et al. **First-line trastuzumab (Herceptin®) plus docetaxel versus docetaxel alone in women with HER2-positive metastatic breast cancer (MBC): Results from a randomised phase II trial (M77001).** *Breast Cancer Res Treat* 2003;82(Suppl):47;Abstract 217.

CALGB-9840: PHASE III STUDY OF WEEKLY VERSUS EVERY THREE-WEEK PACLITAXEL WITH TRASTUZUMAB IN PATIENTS WITH HER2-POSITIVE, METASTATIC BREAST CANCER

Efficacy	Weekly paclitaxel	Every three-week paclitaxel	*p*-value
Tumor response (TR)	40% (n=344)	28% (n=373)	0.017
Time to progression (TTP)	9 months (n=350)	5 months (n=385)	0.0008
Overall survival (OS)	24 months (n=350)	16 months (n=385)	0.17
Efficacy*	**Paclitaxel + trastuzumab**	**Paclitaxel only**	***p*-value**
TR in HER2-normal tumors	35% (n=112)	29% (n=111)	0.34
TTP in HER2-normal tumors	7 months (n=113)	6 months (n=115)	0.09
OS in HER2-normal tumors	22 months (n=113)	20 months (n=115)	0.67
Grade 3-4 toxicities**	**Weekly paclitaxel**	**Every three-week paclitaxel**	***p*-value**
Granulocytopenia	5%	15%	0.013
Neurosensory	23%†	12%	0.001

* Combined weekly plus standard schedules

** Selected, based on any incidence >5%, no significant difference with trastuzumab use

† 19% for patients who did not receive 100 mg/m^2 x 6 initially

SOURCE: Seidman A et al. **Phase III study of weekly paclitaxel via 1-hr infusion vs. standard 3-hr infusion every third week in the treatment of metastatic breast cancer, with trastuzumab for HER2+ MBC and randomized for trastuzumab for HER2 normal MBC.** Presentation. ASCO, 2004.

EXTENSION TRIAL OF TRASTUZUMAB BEYOND DISEASE PROGRESSION IN PATIENTS WITH METASTATIC BREAST CANCER: SAFETY AND EFFICACY DATA

Severe toxicities*	Group 1 Chemotherapy alone in initial trial** (n=153)	Group 2 Chemotherapy + trastuzumab in initial trial† (n=93)
Asthenia	11%	10%
Carcinoma†	8%	12%
Pain	6%	10%
Leukopenia	8%	11%
Efficacy	**Group 1 (n=154)**	**Group 2 (n=93)**
Objective Response (CR+PR)	14% (95% CI, 8.3-19.2)	11% (95% CI, 4.5-17.0)
Clinical benefit (CR+PR+SD)	32%	22%
Median duration of response	7.4 months (95% CI, 5.1-12.5)	6.7 months (95% CI, 4.1-10.2)

CR = complete response; PR = partial response; SD = stable disease >6 months

* Adverse events reported as severe in >5% of treated patients

** Both groups received trastuzumab ± chemotherapy in the extension trial

† Indicative of progressive breast cancer; does not indicate a new cancer

SOURCE: Tripathy D et al. **Safety of treatment of metastatic breast cancer with trastuzumab beyond disease progression.** *J Clin Oncol* 2004;22(6):1063-70.

SELECT PUBLICATIONS

Burris H 3rd et al. **Phase II trial of trastuzumab followed by weekly paclitaxel/carboplatin as first-line treatment for patients with metastatic breast cancer.** *J Clin Oncol* 2004;22(9):1621-9.

Pegram MD et al. **Results of two open-label, multicenter phase II studies of docetaxel, platinum salts, and trastuzumab in HER2-positive advanced breast cancer.** *J Natl Cancer Inst* 2004;96(10):759-69.

Robert NJ et al. **Randomized phase III study of trastuzumab, paclitaxel, and carboplatin versus trastuzumab and paclitaxel in women with HER-2 overexpressing metastatic breast cancer: An update including survival.** *Proc ASCO* 2004;Abstract 573.

Seidman AD et al. **CALGB 9840: Phase III study of weekly (W) paclitaxel (P) via 1-hour(h) infusion versus standard (S) 3h infusion every third week in the treatment of metastatic breast cancer (MBC), with trastuzumab (T) for HER2 positive MBC and randomized for T in HER2 normal MBC.** *Proc ASCO* 2004;Abstract 512.

Slamon DJ 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.

Tedesco KL et al. **Docetaxel combined with trastuzumab is an active regimen in HER-2 3+ overexpressing and fluorescent in situ hybridization-positive metastatic breast cancer: A multi-institutional phase II trial.** *J Clin Oncol* 2004;22(6):1071-7.

Tripathy D et al. **Safety of treatment of metastatic breast cancer with trastuzumab beyond disease progression.** *J Clin Oncol* 2004;22(6):1063-70.

Vogel CL et al. **Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer.** *J Clin Oncol* 2002;20(3):719-26.

Yardley DA et al. **First line treatment with weekly docetaxel, vinorelbine, and trastuzumab in HER2 overexpressing metastatic breast cancer (HER2+ MBC): A Minnie Pearl Cancer Research Network phase II trial.** *Proc ASCO* 2004;Abstract 643.

TRASTUZUMAB ALONE OR WITH CHEMOTHERAPY

I use trastuzumab alone in a minority of patients — usually elderly women or young women who are not willing to undergo another course of chemotherapy — but I prefer combination therapy. In patients who have had a prior response to chemotherapy and trastuzumab and are now receiving trastuzumab alone but have disease progression, I continue trastuzumab and reintroduce chemotherapy for three to four months. I have seen nice responses in those situations.

If the treatment-free interval was long, I might use the initial chemotherapy, but if it was six months or less I would select a different agent. We have strong data supporting the use of taxanes in combination with trastuzumab. A recent trial comparing docetaxel with or without trastuzumab had striking results favoring the combination. I believe it is a good regimen to choose. If I were to use paclitaxel, I would administer it weekly with trastuzumab. I have also seen impressive anecdotal responses to vinorelbine plus trastuzumab.

— Martine J Piccart-Gebhart, MD, PhD

I discuss the data on combination and single-agent trastuzumab and tell patients that we don't know if it is better to give the combination up front or if there is any harm in giving trastuzumab alone and then adding the chemotherapy at progression. Generally, in a patient with life-threatening disease, I'm going to go for the best response and will recommend giving chemotherapy with trastuzumab. But for patients who have pretty low-volume or quiescent disease and are not symptomatic, or older patients in whom cardiac problems may arise, I think trastuzumab monotherapy is a reasonable option.

— Julie R Gralow, MD

The *in vitro* synergy between the platinums and trastuzumab has recently been put to the test. The results of Dr Nicholas Robert's study were remarkable. In the patients who received carboplatin in addition to trastuzumab/paclitaxel, the response rates and the time to progression were significantly improved.

— Mark D Pegram, MD

TRIAL OF TRASTUZUMAB BEYOND PROGRESSION

"…some patients who experience disease progression may respond to or derive a clinical benefit from additional trastuzumab-based therapy, although the magnitude of the benefit is also consistent with the effect of salvage chemotherapy alone.

"The durations of response in both groups exceeded 6 months, slightly shorter than has been seen on first exposure to trastuzumab when used as a single agent or in combination with chemotherapy. Because HER2-positive cancer is associated with an aggressive clinical course, these results may represent promising activity in this population refractory to prior chemotherapy regimens, including trastuzumab."

— Tripathy D et al. J Clin Oncol *2004;22(6):1063-70.*

SAFETY OF TRASTUZUMAB BEYOND PROGRESSION

"The extension trial described in this report was undertaken to provide trastuzumab therapy to patients whose metastatic breast cancer progressed during treatment with chemotherapy with or without trastuzumab. It was designed primarily to provide additional safety information regarding the addition of trastuzumab to various chemotherapeutic agents. …

"No new specific adverse events were seen with any particular chemotherapy regimen or with prolonged administration of trastuzumab of up to 40 months, suggesting that long-term trastuzumab treatment is well tolerated. No cumulative toxicities emerged over this time frame. …

"Although treatment beyond progression would represent a new paradigm in oncologic therapy, the novel and targeted activity of trastuzumab, including direct antiproliferative activity, synergistic interaction with a number of standard chemotherapy agents, and antiangiogenic activity, may support this approach."

— Tripathy D et al. J Clin Oncol *2004;22(6):1063-70.*