

# Response of Prostate Cancer to Anti-Her-2/neu Antibody in Androgen-dependent and -independent Human Xenograft Models<sup>1</sup>

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## Abstract

Antibody to the Her-2/neu gene product has been shown to inhibit the growth of breast cancer cells overexpressing Her-2/neu and to have clinical utility in treating breast cancer. We studied a recombinant, humanized anti-Her-2/neu antibody (Herceptin) in preclinical models of human prostate cancer. The androgen-dependent CWR22 and LNCaP human prostate cancer xenograft models and androgen-independent sublines of CWR22 were used. Her-2/neu staining of the parental, androgen-dependent, and androgen-independent CWR22 tumors and LNCaP tumors demonstrated variable Her-2/neu expression. Herceptin was administered i.p. at a dose of 20 mg/kg twice weekly after the xenograft had been established. No effect of Herceptin on tumor growth was observed in any of the androgen-independent tumors; however, significant growth inhibition was observed in both of the androgen-dependent xenograft models, CWR22 (68% growth inhibition at the completion of the experiment;  $P = 0.03$  for trajectories of the average tumor volume of the groups) and LNCaP (89% growth inhibition;  $P = 0.002$ ). There was a significant increase in prostate-specific antigen (PSA) index (ng PSA/ml serum/mm<sup>3</sup> tumor) in Herceptin-treated androgen-dependent groups compared with control (CWR22, 18-fold relative to pretreatment value versus 1.0-fold,  $P = 0.0001$ ; LNCaP, 2.35-fold relative to pretreatment value versus 0.6-fold,  $P = 0.001$ ). When paclitaxel (6.25 mg/kg s.c., five times/week) was given to animals with androgen-dependent and -independent tumors, there was growth inhibition in each group. Paclitaxel and Herceptin cotreatment led to greater growth inhibition than was seen for the agents individually. Thus, in these prostate cancer model systems, Herceptin alone has clinical activity only in the androgen-dependent tumor and has at least an additive effect on growth, in combination with paclitaxel, in both androgen-dependent and androgen-independent tumors. Response to Herceptin did not correlate with the PSA levels, because the PSA index markedly increased in the Herceptin-treated group, whereas it remained constant in the control group. These results suggest the utility of Herceptin in the treatment of human prostate cancer.

## Introduction

Her-2/neu is overexpressed in 25–30% of human breast and ovarian cancers and predicts for a poor prognosis in breast cancer patients (1–3). Antibodies to the extracellular domain of Her-2/neu (gp185) can inhibit the growth of tumor xenografts and transformed cells that express high levels of this tyrosine kinase receptor (4–7). A recombinant, humanized mAb<sup>3</sup> anti-P185<sup>Her-2/neu</sup> (Herceptin) has a cytostatic growth-inhibitory effect on breast cancer cells overexpressing

Her-2/neu (8) and has been demonstrated to enhance the antitumor activity of paclitaxel and doxorubicin against Her-2/neu-overexpressing human breast cancer xenografts (9, 10). This antibody has clinical activity in breast cancer patients with metastatic disease overexpressing Her-2/neu (11) and has demonstrated clinical activity when combined with paclitaxel in patients with breast cancer. Because Her-2/neu may be overexpressed in prostate cancer (12–15), we examined the effect of Herceptin monotherapy in androgen-dependent (CWR22 and LNCaP) and androgen-independent (CWR22 derivatives) prostate cancer xenograft models (16–18) and the combination of Herceptin with paclitaxel. Our results indicate that clinical trials of Herceptin in human prostate cancer are warranted.

## Materials and Methods

**Animal Studies.** Four to six-week-old nude athymic BALB/c male and female mice were obtained from the National Cancer Institute-Frederick Cancer Research & Development Center and maintained in pressurized ventilated caging at the Sloan-Kettering Institute. Male animals were inoculated s.c. with  $1 \times 10^6$  LNCaP cells or minced tumor tissue from the androgen-dependent CWR22 cell line, and females received the androgen-independent sublines CWR22R, WR22SA1, CWRSA4, or CWRSA6, which were obtained by selecting tumors for regrowth and increased serum PSA after androgen withdrawal. All cell lines were injected together with reconstituted basement membrane (Matrigel; Collaborative Research, Bedford, MA), as described previously (16, 17, 19). To maintain serum testosterone levels, male mice were implanted with 12.5-mg sustained release testosterone pellets (Innovative Research of America, Sarasota, FL) s.c. before receiving the tumor cell inoculation. Treatments consisted of a twice weekly i.p. injection of 20 mg/kg Herceptin (recombinant, humanized mAb Her2; Genentech, Inc., South San Francisco, CA) in PBS for no less than 3 weeks and/or paclitaxel (Taxol; Bristol Myers-Squibb Co., Princeton, NJ) low dose (6.25 mg/kg s.c., five times/week  $\times$  3 weeks) or high dose (12.5 mg/kg s.c., five times/week  $\times$  2 weeks) in sterile saline. Control mice were given vehicle alone. Tumors were measured every 3–4 days with vernier calipers, and tumor volumes were calculated by the formula  $\pi/6 \times \text{larger diameter} \times (\text{smaller diameter})^2$  (Ref. 2). Animals with palpably established tumors of at least 65 mm<sup>3</sup> in volume were designated to treatment groups.

**Determination of the Her-2/neu Status of the Xenografts.** Xenografts were assayed for Her-2/neu expression by immunohistochemistry using the DAKO Her-2 kits (HercepTest; DAKO Corp., Carpinteria, CA). The samples were scored blindly by comparison with standard controls in the DAKO kit standards and scored as follows: (a) 0, no staining or membrane staining in <10% of the tumor cells; (b) 1<sup>+</sup>, faint membrane staining in >10% of the tumor cells; (c) 2<sup>+</sup>, weak to moderate complete membrane stain in >10% of cells; or (d) 3<sup>+</sup>, moderate to strong complete membrane staining in >10% of cells. A score of 0 or 1<sup>+</sup> was considered negative for Her-2/neu overexpression, whereas 2<sup>+</sup> or 3<sup>+</sup> indicated Her-2/neu overexpression. FISH analysis was done using the Oncor kits (Inform Her-2/neu gene detection system; Oncor, Gaithersburg, MD). A minimum of 100 tumor cells in each tumor were evaluated for nuclear Her-2/neu gene copy number (13).

**Determination of Serum PSA Values.** Blood samples (~50  $\mu$ l) from male mice collected in microtainer serum separator tubes (Becton Dickinson, Franklin Lakes, NJ) by superficial incision of the dorsal tail vein were taken

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<sup>3</sup> The abbreviations used are: mAb, monoclonal antibody; PSA, prostate-specific antigen; FISH, fluorescence *in situ* hybridization.

before therapy and on days 9 and 21 of treatment. PSA values were then determined from the serum using the Tandem-R PSA immunoradiometric assay (Hybritech, San Diego, CA).

**Statistical Analysis.** Pairwise differences between the tumor volumes of the treatment groups were compared over time using a permutation test. The null hypothesis for this test is that treatment has no differential effect on the tumor volumes over time. The statistic used to test the hypothesis was the sum of the squared differences between mean tumor volume summed over all time points.

$$SS\_DEV = \sum_{i=1}^k (\bar{x}_i - \bar{y}_i)^2$$

SS\_Dev was used to capture the average differences between treatment groups at each time point. This statistic reflects the amount by which the trajectories of average tumor volume of the two treatment groups are different.

## Results

**Her-2/neu Immunohistochemical Staining and Her-2 Gene Copy Number of the Prostate Xenografts.** The Her-2 expression patterns of the androgen-dependent and androgen-independent prostate xenografts were examined by immunohistochemistry and FISH. The parental androgen-dependent CWR22 tumors demonstrated 2<sup>+</sup> Her-2/neu staining, and the LNCaP tumors demonstrated 3<sup>+</sup> Her-2/neu staining (Fig. 1, A and B). The androgen-independent sublines of CWR22 demonstrate 2<sup>+</sup> (CWRSA1), 3<sup>+</sup> (CWRSA4), 2<sup>+</sup>

(CWRSA6), and 1<sup>+</sup> (CWR22R) staining for Her-2/neu (Fig. 1, C–F). All tumors had a 2–4 Her-2/neu gene copy (normal range) number by FISH (data not shown).

**Effects of Herceptin on Established Prostate Cancer Xenografts.** We evaluated the efficacy of Herceptin in well-established androgen-dependent and androgen-independent prostate cancer xenografts. The CWR22, LNCaP, CWR22R, and CWRSA6 models were used for these experiments because they provided reproducible growth curves. Herceptin (20 mg/kg twice weekly) had no effect on the tumor growth curve in any of the androgen-independent tumors when compared to control (CWR22R,  $P = 0.60$ ,  $n = 10$ , Fig. 2A; CWRSA6,  $P = 0.63$ ,  $n = 10$ , Fig. 2B). The murine anti-Her-2 mAb, 4D5, also had no effect on tumor growth in the CWR22R androgen-independent cell line ( $P = 0.21$ ,  $n = 10$ ; data not shown). In contrast, Herceptin did show significant growth inhibition of both of the androgen-dependent xenograft models, CWR22 (68% growth inhibition,  $P = 0.03$ ,  $n = 12$ , Fig. 2C) and LNCaP (89% growth inhibition,  $P = 0.002$ ,  $n = 12$ , Fig. 2D). The histology of the tumors in each group was examined by light microscopy, and no visible difference in necrosis was seen between the groups (data not shown).

**Effects of Herceptin Combined with Paclitaxel on Established Tumor Xenografts.** Graded doses of paclitaxel were administered to the xenograft-bearing animals to determine a dosage of paclitaxel that inhibited growth but did not cause complete regression of the tumors (data not shown). Paclitaxel at a dosage of 6.25 mg s.c. five times/

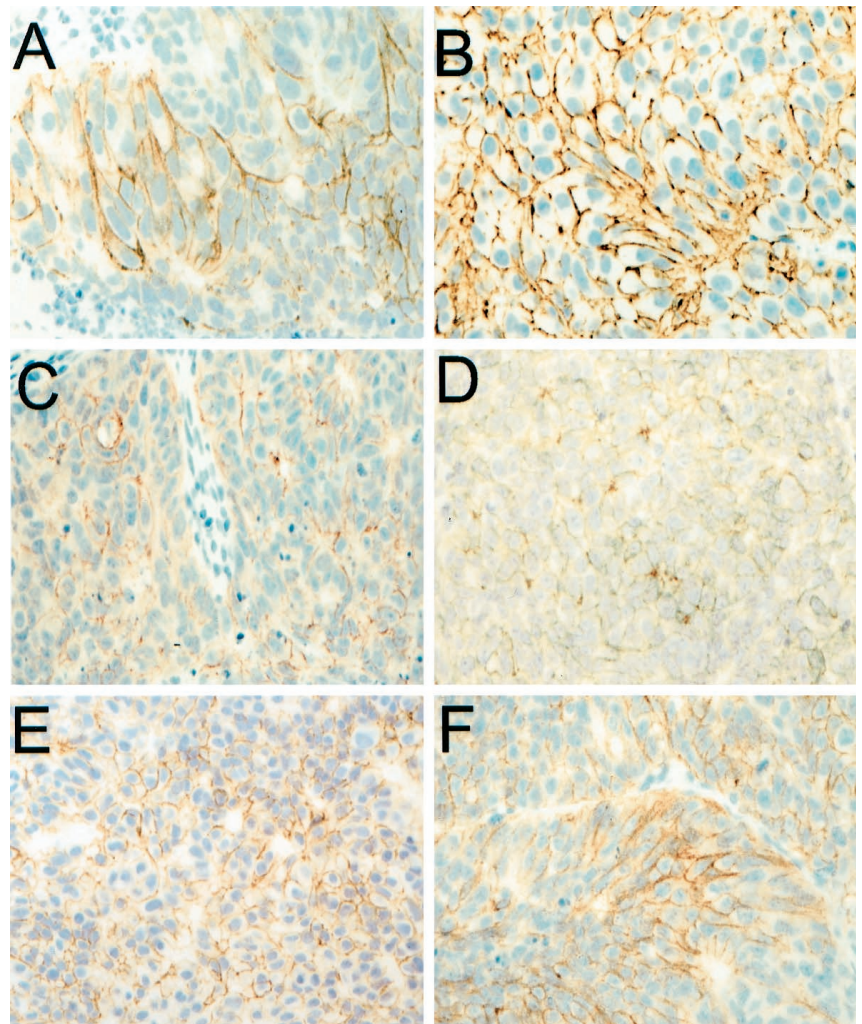


Fig. 1. Photomicrographs of immunocytochemistry sections of tumors from a nude mouse with human prostate cancer xenografts stained with an anti-Her-2/neu mAb ( $\times 400$ ). Representative areas of sections from the tumors are as follows: A, CWR22; B, LNCaP; C, CWR22R; D, CWRSA1; E, CWRSA4; F, CWRSA6.

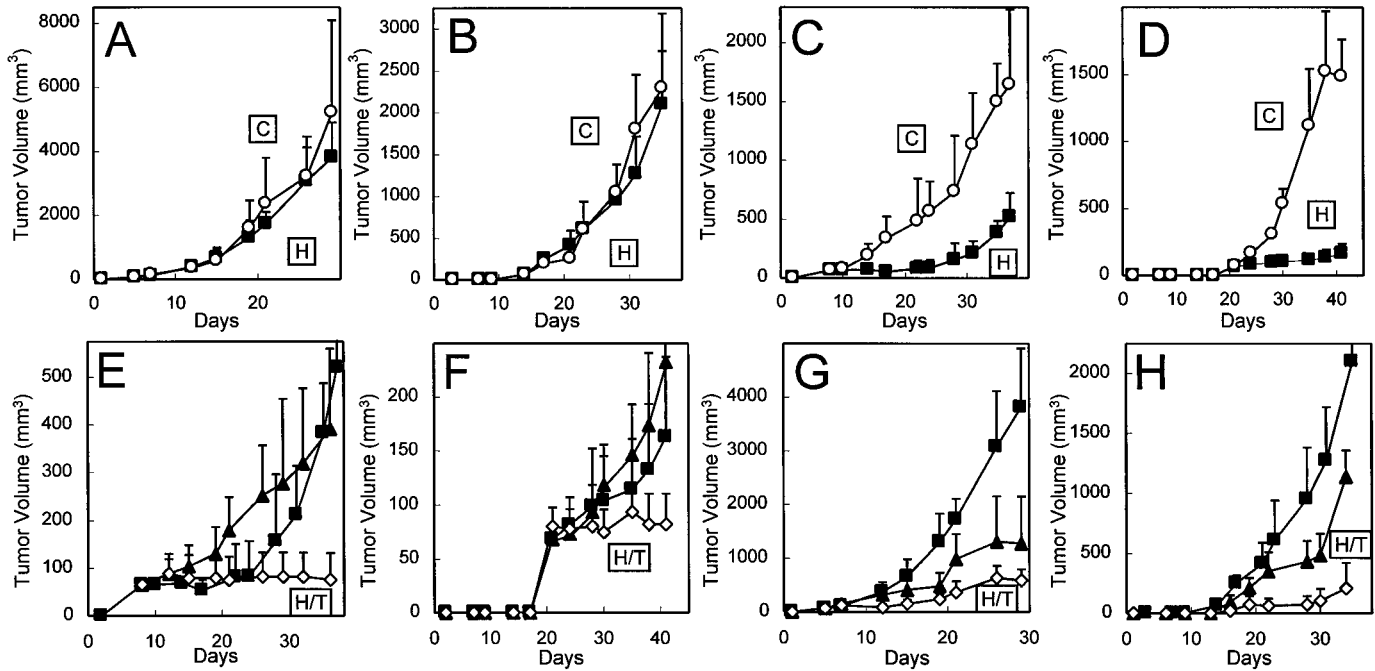


Fig. 2. Response of xenograft tumors to Herceptin (H, ■), control (C, ○), and paclitaxel (T, ▲) and combination Herceptin/paclitaxel (H/T, ◇) treatment. The response of androgen-independent tumors (A) CWR22R and (B) CWRSA6 and androgen-dependent tumors (C) CWR22 and (D) LNCaP to Herceptin and control are shown. The response of the tumors to Herceptin, paclitaxel, Herceptin/paclitaxel, and control are shown in E (CWR22), F (LNCaP), G (CWR22R), and H (CWRSA6). Results are given as mean tumor volume  $\pm$  SE.

week given to animals with well-established tumors caused growth inhibition as compared to control at the time of the sacrifice (CWR22, 76% growth inhibition,  $P = 0.02$ , Fig. 2E; LNCaP, 84% growth inhibition,  $P = 0.002$ , Fig. 2F; CWR22R, 76% growth inhibition,  $P = 0.02$ , Fig. 2G; CWRSA6, 51% growth inhibition,  $P = 0.02$ , Fig. 2H). When paclitaxel and Herceptin were coadministered to animals, there was a marked reduction in tumor volume *versus* control for both androgen-dependent and androgen-independent tumors (CWR22, 98% growth inhibition,  $P = 0.01$ , Fig. 2E; CWR22R, 92% growth inhibition,  $P = 0.01$ , Fig. 2G; LNCaP, 94% growth inhibition,  $P = 0.006$ , Fig. 2F; CWRSA6, 77% growth inhibition,  $P = 0.01$ , Fig. 2H). Increased growth inhibition was observed with the combination of Herceptin and paclitaxel as compared to each agent alone at the end of the treatment period in the animals with androgen-dependent xenografts (Fig. 2, E–H), the CWR22 group [mean tumor volumes ( $n = 6$  in each group): paclitaxel, 408 mm<sup>3</sup>; Herceptin, 520 mm<sup>3</sup>; paclitaxel and Herceptin, 76 mm<sup>3</sup>; paclitaxel *versus* paclitaxel and Herceptin,  $P = 0.03$ ] and the LNCaP group [mean tumor volumes ( $n = 6$  in each group): paclitaxel, 233 mm<sup>3</sup>; Herceptin, 163 mm<sup>3</sup>; paclitaxel and Herceptin, 82 mm<sup>3</sup>; paclitaxel *versus* paclitaxel and Herceptin,  $P = 0.03$ ]. In addition, there was increased growth inhibition with the combination of Herceptin and paclitaxel *versus* each agent alone at the end of the treatment period in the animals with androgen-independent xenografts (Fig. 2, E–H), the CWRSA6 group [mean tumor volumes ( $n = 5$  in each group): paclitaxel, 1496 mm<sup>3</sup>; Herceptin, 2941 mm<sup>3</sup>; paclitaxel, and Herceptin, 687 mm<sup>3</sup>; paclitaxel *versus* paclitaxel and Herceptin,  $P = 0.001$ ] and the CWR22R group [mean tumor volumes ( $n = 5$  in each group): paclitaxel, 1273 mm<sup>3</sup>; Herceptin, 3811 mm<sup>3</sup>; paclitaxel and Herceptin, 592 mm<sup>3</sup>; paclitaxel *versus* paclitaxel and Herceptin,  $P = 0.095$ ].

The lack of clinical activity of Herceptin in the androgen-independent models could indicate a requirement for androgen to be present for the Herceptin antitumor response to be manifested. Therefore, androgen pellets were added to the androgen-independent models

(CWR22R and CWRSA6). The response to Herceptin and Herceptin with paclitaxel was no different from that in the absence of androgen (data not shown).

**Effect of Herceptin on the PSA Index in Animals with Androgen-dependent Xenografts.** The PSA index (ng PSA/ml serum/mm<sup>3</sup> tumor) was measured in the androgen-dependent animals at the time treatment was initiated (day = 0) and at days 9 and 21 of treatment. There was a significant increase in the PSA index in Herceptin-treated androgen-dependent animals at both time points when compared with pretreatment values, whereas the control animals showed a decrease in the PSA index at either time point when compared to day 0 [LNCaP, control 0.6 relative to pretreatment value; Herceptin group, 2.35 relative to pretreatment value at day 21 (Fig. 3A); CWR22, control 1.0 relative to pretreatment value; Herceptin group, 18 relative to pretreatment value at day 21 (Fig. 3B)]. The relative PSA index decreased in the LNCaP untreated group possibly secondary to increased necrosis with increasing tumor size, although this was not detectable by light microscopy. There was also an increase in the PSA index after combination treatment with Herceptin and paclitaxel when compared with pretreatment values (data not shown).

## Discussion

We found that Herceptin alone has antitumor activity in the androgen-dependent human prostate cancer xenograft models studied and has at least an additive effect in combination with paclitaxel in inhibition of tumor growth. Herceptin alone had no demonstrable antitumor effect in the androgen-independent models but clearly enhanced the activity of paclitaxel. The response to Herceptin alone appears to require the presence of androgen and/or that the tumor itself be androgen dependent. The lack of response of the androgen-independent tumors to Herceptin in the presence of androgen indicates that androgen dependence or the requirement for signaling through the androgen receptor is a necessary element for Herceptin response in these prostate tumors.

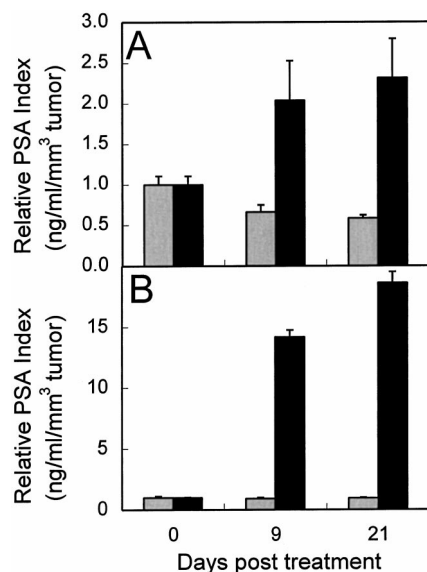


Fig. 3. Relative PSA index response of animals with androgen-dependent prostate cancer xenografts treated with Herceptin. A, PSA index was measured in the LNCaP xenograft model before treatment and at days 9 and 21 after initiating treatment and expressed relative to pretreatment values (■, treatment group; □, control group). B, PSA index was measured in the CWR22 xenograft model before treatment and at days 9 and 21 after initiating treatment and expressed relative to pretreatment values (■, treatment group; □, control group). Results are given as mean relative PSA index  $\pm$  SE.

It has recently been shown that overexpression of Her-2/neu can allow androgen-independent growth in LNCaP xenograft models (20). All of the androgen-independent xenografts used in our studies expressed androgen receptor, as assayed by immunohistochemistry (data not shown). The prostate cancer models used in this study overexpress Her-2/neu on the cell surface. The expression of functional androgen receptor, coupled with the overexpression of Her-2/neu in the parental CWR22 cell line, suggests that Her-2/neu is not expressed because of androgen insensitivity in these tumors. The lack of response to Herceptin in the androgen-independent tumors suggests that the androgen signaling pathway in the androgen-dependent models may be permissive with regard to Herceptin response. The basis for the ability of Herceptin to enhance the paclitaxel antitumor effect in androgen-independent prostate cancer is uncertain. It is possible that Herceptin initiates or impairs cell signaling pathways that allow for increased paclitaxel cell kill. Other mechanisms for this effect may be immunological, or Herceptin may affect the tumor concentration of paclitaxel.

Growth inhibition in the androgen-dependent tumors by Herceptin was accompanied by an increased PSA index when compared with pretreatment values. In contrast, the control-treated animals showed a decrease in the PSA index with time. Her-2/neu overexpression in prostate cancer cells may cause androgen-independent growth by activation of the androgen receptor signaling pathway in a ligand-independent fashion (20). In our model systems, Herceptin binding to Her-2/neu led to increased cellular secretion of PSA in an androgen-independent fashion. This result further supports the notion of cross-talk between the Her-2/neu and androgen receptor signaling pathways. The lack of correspondence between the PSA index and tumor response will complicate clinical trial design, which routinely uses PSA as a surrogate for tumor response. Clinical trials are currently underway examining the role of Herceptin in human prostate cancer using end points other than PSA.

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