for anti-metastatic activity per se. On the contrary, enhanced metastasis has been observed in response to several anti-cancer drugs (Geldof, A. A., et al., Anticancer Res. 8 (1988) 1335-1339; Murphy, S. B., J. Clin. Oncol. 11 (1993) 199-201; and De Larco,J. E., et al., Cancer Res. 61 (2001) 2857-2861). Clearly there exists a need to develop treatment therapies that target not only the primary tumor, but also suppress metastasis.

Summary ~~of the Invention~~

The disclosure~~invention~~ comprises the use of an anti-HER2 antibody and an anti-VEGF antibody for the manufacture of a medicament for treating a breast cancer disease in a patient who has failed prior therapy with an anti-VEGF antibody, comprising administering to the patient a therapeutically effective amount of an anti-HER2 antibody and an anti-VEGF antibody.

In one aspect, there is provided the use of an anti-HER2 antibody and an anti-VEGF antibody for the manufacture of a medicament for treating a breast cancer disease characterized by an overexpression of the HER2 receptor protein in a patient who has failed prior therapy with an anti-VEGF antibody, by administration to the patient of a therapeutically effective amount of the anti-HER2 antibody and the anti-VEGF antibody, wherein the anti-HER2 antibody and the anti-VEGF antibody are for separate or simultaneous administration.

In a preferred embodiment, the disclosure~~invention~~ comprises the use of trastuzumab and bevacizumab for the manufacture of a medicament for treating a breast cancer disease characterized by an overexpression of the HER2 receptor protein in a patient who has failed prior therapy with an anti-VEGF antibody such as bevacizumab, comprising administering to the patient a therapeutically effective amount of trastuzumab and bevacizumab.

The disclosure~~invention~~ further comprises a method of treating a breast cancer disease in a patient who has failed prior therapy with an anti-VEGF antibody, comprising administering to the patient a therapeutically effective amount of an anti-HER2 antibody while continuing said anti-VEGF antibody therapy.

The disclosure~~invention~~ further comprises a method of treating a breast cancer disease, characterized by an overexpression of the HER2 receptor protein, in a patient who has failed prior therapy with an anti-VEGF antibody, comprising administering to the patient a therapeutically effective amount of trastuzumab while continuing bevacizumab therapy.

The disclosure~~invention~~ further comprises a method for increasing the duration of survival of a patient having breast cancer disease who has failed prior therapy with an anti-VEGF antibody, comprising administering to the patient effective amounts of an anti-VEGF antibody and an anti-HER2 antibody, whereby the co-administration of the anti-VEGF antibody and the anti-HER2 antibody effectively increases the duration of survival.

The disclosure~~invention~~ further comprises a method for increasing the progression free survival of a patient having breast cancer disease who has failed prior therapy with an anti-VEGF antibody, comprising administering to the patient effective amounts of an anti-VEGF antibody and an anti-HER2 antibody, whereby the co-administration of the anti-VEGF antibody and the anti-HER2 antibody effectively increases the duration of progression free survival.

The disclosure~~invention~~ further comprises a method for treating a group of patients, having breast cancer disease and having failed prior therapy, with an anti-VEGF antibody, comprising administering to the patient effective amounts of an anti-VEGF antibody and an anti-HER2 antibody, whereby the co-administration of the anti-VEGF antibody and the anti-HER2 antibody effectively increases the response rate in the group of patients.

The disclosure~~invention~~ further comprises a method for increasing the duration of response of a patient having breast cancer disease who has failed prior therapy with an anti-VEGF antibody, comprising administering to the patient effective amounts of an anti-VEGF antibody and an anti-HER2 antibody, whereby the co-administration of the anti-VEGF antibody and the anti-HER2 antibody effectively increases the duration of response.

The disclosure~~invention~~ further comprises a method of treating a patient having breast cancer disease who has failed prior therapy with an anti-VEGF antibody, comprising administering to the patient effective amounts of an anti-VEGF antibody and an anti-HER2 antibody, whereby the co-administration of the anti-VEGF antibody and the anti-HER2 antibody results in statistically significant and clinically meaningful improvement of the treated patient as measured by the duration of survival, progression free survival, response rate or duration of response.

This disclosure~~invention~~ further comprises a method for reducing metastasis in a patient having breast cancer disease who has failed prior therapy with an anti-VEGF antibody, comprising administering to the patient effective amounts of an anti-VEGF antibody and an anti-HER2 antibody, whereby the co-administration of the anti-VEGF antibody and the anti-HER2 antibody effectively reduces metastasis.

The disclosure~~invention~~ further comprises a method for treating a group of patients, having breast cancer disease and having failed prior therapy, with an anti-VEGF antibody, comprising administering to the patient effective amounts of an anti-VEGF antibody and an anti-HER2 antibody, whereby the co-administration of the anti-

VEGF antibody and the anti-HER2 antibody effectively reduces metastasis in the group of patients.

The disclosure~~invention~~ provides an article of manufacture comprising a container, a composition within the container comprising an anti-VEGF antibody and a package insert instructing the user of the composition to administer to a patient, having breast cancer disease who has failed prior therapy with an anti-VEGF antibody, the anti-VEGF antibody and an anti-HER2 antibody.

The disclosure~~invention~~ further provides an article of manufacture comprising a container, a composition within the container comprising an anti-HER2 antibody and a package insert instructing the user of the composition to administer to a patient, having breast cancer disease who has failed prior therapy with an anti-VEGF antibody, the anti-HER2 antibody and an anti-VEGF antibody.

The disclosure~~invention~~ further provides for a composition comprising an anti-HER2 antibody and an anti-VEGF antibody useful in the treatment of breast cancer disease in a patient which has failed prior therapy with an anti-VEGF antibody. Preferably the anti-HER2 antibody is trastuzumab. Also preferably the anti-VEGF antibody is bevacizumab.

Brief Description of the Drawings

Figure 1 Antitumor activity of combined trastuzumab and bevacizumab treatment on tumor growth after bevacizumab treatment failure. Mean values of tumor volume (mm^3) plotted on the y-axis; number of days after injection of tumor cells plotted on the x-axis. Vehicle (*circles*), trastuzumab at loading dose of 30mg/kg and maintenance dose of 15mg/kg (*squares*), bevacizumab at 5mg/kg until day 55 when treatment also includes trastuzumab at 15mg/kg (*triangles*).

Figure 2 Effect of combined trastuzumab and bevacizumab treatment on lung metastasis. Mean value of human Alu DNA sequence (ng/ml) quantitated from lung tissue using real-time PCR and plotted on the y-axis.