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Legal Manufacturer

Siemens Healthcare Diagnostics Inc.
1717 Deerfield Road
Deerfield, IL 60015-0778
USA

Global Division

Siemens Healthcare Diagnostics Inc.
1717 Deerfield Road
Deerfield, IL 60015-0778
USA
www.siemens.com/diagnostics

Siemens Global Headquarters

Siemens AG
Wittelsbacherplatz 2
80333 Muenchen
Germany

Global Siemens Healthcare Headquarters

Siemens AG
Healthcare Sector
Henkestrasse 127
91052 Erlangen
Germany
Telephone: +49 9131 84 - 0
www.siemens.com/healthcare

www.siemens.com/diagnostics



Understanding the Clinical Utility of Serum HER-2/neu

Answers for life.

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Current Advances in HER-2/neu Biomarker Testing

Follow HER-2/neu for Life

Serum HER-2/neu is a blood test for more precise management of HER-2/neu metastatic breast cancer patients and for monitoring the effectiveness of therapy.

These clinical references highlight data indicating that serum levels of HER-2/neu reflect disease progression and response to therapy, and that serial monitoring of Serum HER-2/neu may be a valuable tool in creating a more efficient treatment regimen.

Serum HER-2/neu change predicts clinical outcome to trastuzumab-based therapy

Ali SM, Esteva FJ, Fournier M, et al. J Clin Oncol, ASCO Annual Meeting Proceedings Part 1, 2006;24(18S, 6/20 Supplement);Abstract No. 500.

In this report, Ali et al. presented data from seven clinical institutions and 307 metastatic breast cancer (MBC) patients who had the Serum HER-2/neu test before and after treatment (30-120 days) with trastuzumab-based therapy.

The results of this study allowed the 307 MBC patients who had the Serum HER-2/neu test before and after trastuzumab-based treatment to be divided into those with a greater than 20 percent decrease from baseline to first follow-up visit and those with a less than 20 percent decrease from baseline to the first follow-up visit. The patients whose Serum HER-2/neu levels decreased by less than 20 percent had a lower response rate; shorter duration of response; shorter time to progression; and decreased overall survival rate. The authors concluded that patients with <20% change from baseline should be considered for investigative agents in addition to trastuzumab.

Monitoring of Serum HER-2/neu predicts response and progression-free survival to trastuzumab-based treatment in patients with metastatic breast cancer

Koestler WJ, Schwab B, Singer CF, Neumann R, Rucklinger E, Brodowicz T, Tomek S, Niedermayr M, Hejna M, Steger GG, Krainer M, Wiltshcke C, Zielinski CC. Clin Cancer Res 2004;10(5):1618-1624.

This study was performed to determine if early changes in Serum HER-2/neu levels during trastuzumab-based treatment would predict the clinical course of disease in patients with metastatic breast cancer. In patients responding to treatment,



Serum HER-2/neu levels decreased significantly as early as day eight of treatment onward. In contrast, no significant change in Serum HER-2/neu levels was observed in patients with progressive disease. Multiple logistic regression analyses identified kinetics of Serum HER-2/neu levels as the only factor that allowed for the accurate prediction of response likelihood as early as from day eight of trastuzumab-based treatment onward. In addition, determination of serial HER-2/neu levels allowed for the prediction of the risk for disease progression within the observed period as early as day 15 of treatment.

Clinical utility of Serum HER-2/neu in monitoring and prediction of progression-free survival in metastatic breast cancer patients treated with trastuzumab-based therapies

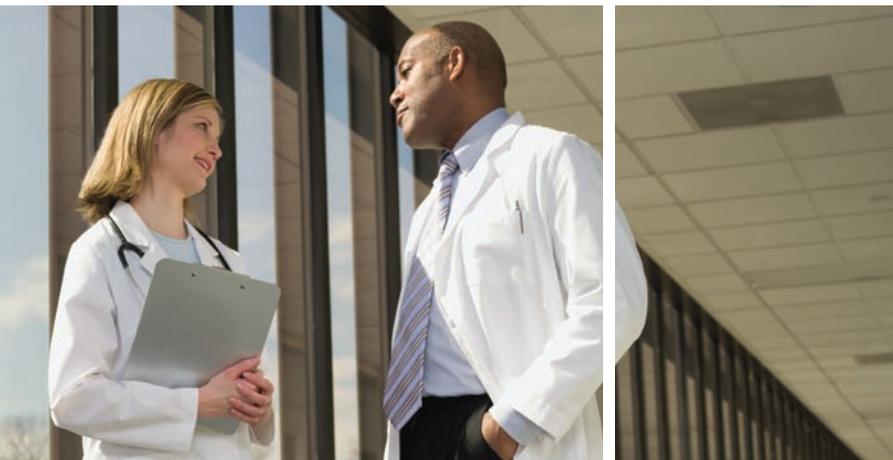
Esteva FJ, Cheli CD, Fritsche H, Fornier M, Slamon D, Thiel RP, Lueftner D, Ghani F. Breast Cancer Res 2005;7(4):R436-443.

The purpose of this retrospective study was to determine the clinical utility of Serum HER-2/neu in monitoring metastatic breast cancer patients undergoing trastuzumab-based therapy and to compare these results with those obtained using cancer antigen (CA) 15-3. Sera were obtained retro-

spectively from 103 women at four medical institutions. A baseline serum sample for each patient was taken before trastuzumab-based therapy was started. Patients were subsequently monitored over 12 to 20 months and serum samples were taken at the time of clinical assessment and tested with the Serum HER-2/neu or CA 15-3 tests.

Progression-free survival differed significantly ($P = 0.043$) according to whether the patient's HER-2/neu concentration at 2 to 4 weeks after the start of therapy was $>77\%$ or $\leq 77\%$ of her baseline level. The median progression-free survival times for these two groups were 217 and 587 days, respectively.

These findings indicate that Serum HER-2/neu testing is clinically valuable in monitoring metastatic breast cancer patients undergoing trastuzumab-based treatment and provides additional value over the commonly used CA 15-3 test. The investigators concluded that the percentage of baseline HER-2/neu concentrations in the early weeks after the start of therapy may be an early predictor of progression-free survival.



Serum HER-2 extracellular domain in metastatic breast cancer patients treated with weekly trastuzumab and paclitaxel

Fornier MN, Seidman AD, Schwartz MK, et al. Ann Oncol 2005;16(2): 234-239.

In this report, the investigators examined the relationship between Serum HER-2/neu levels and tissue HER-2 status as determined by immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH). They also examined the predictive value of Serum HER-2/neu in a cohort of metastatic breast cancer patients treated with weekly trastuzumab and paclitaxel.

In this study, the investigators reported a statistically significant association between pretreatment Serum HER-2/neu levels and tissue HER-2/neu status as assessed by IHC and FISH. A decrease in Serum HER-2/neu levels of over 55 percent from baseline was a significant predictor of response to trastuzumab-based therapy.

Serum HER-2/neu conversion to positive at the time of disease progression in patients with breast carcinoma on hormone therapy

Lipton A, Leitzel K, Ali SM, et al. Cancer 2005;104(2): 257-263.

This study found that conversion to an elevated Serum HER-2/neu level (15 ng/mL or greater) occurred in approximately 26 percent of patients who received first-line hormone therapy with letrozole or tamoxifen. Conversion to Serum HER-2/neu-elevated status with antiestrogen and aromatase-inhibitor therapy produced equal results. Serum conversion to HER-2/neu-positive status was shown to be an independent risk factor for decreased survival in breast carcinoma patients.

Serum HER-2/neu in the management of breast cancer patients

Lueftner D, Luke C, Possinger K. Clin Biochem 2003;36(4):233-240.

This review notes that Serum HER-2/neu levels are elevated beyond normal in 50 to 60 percent of stage IV breast cancer patients. The review also concludes that in longitudinal follow-up of patients during any kind of systemic therapy, Serum HER-2/neu testing is complementary to HER-2/neu tissue results.

The course of Serum HER-2/neu levels as an independent prognostic factor for survival in metastatic breast cancer

Schippinger W, Regitnig P, Bauernhofer T, Ploner F, Hofmann G, Krippel P, Wehrschutz M, Lax S, Carney W, Neumann R, Wernecke KD, Samonigg H. Oncol Rep 2004;11(6): 1331-1336.

In this study, patients with continuously elevated Serum HER-2/neu levels had a significantly poorer survival after disease recurrence compared to patients with continuously or temporarily nonelevated Serum HER-2/neu levels. The study concluded that decrease of elevated Serum HER-2/neu to levels below 15 ng/mL and levels continuously ≤ 15 ng/mL during the course of disease correlated significantly with longer survival.

HER-2/neu Summary Reviews

The following reviews summarize clinical experience with Serum HER-2/neu testing to date, current clinical utility, and possible future directions.

Monitoring the circulating levels of the HER-2/neu oncoprotein in breast cancer

Carney WP, Neumann R, Lipton A, Leitzel K, Ali S, Price CP. Clin Breast Cancer 2004;5(2):105-116.

This review notes that the percentage of women with elevated Serum HER-2/neu due to the presence of a HER-2/neu-positive tumor is higher than generally known. Studies show on average that approximately

45.6 percent (range 23-80 percent) of patients with metastatic breast cancer have an elevated Serum HER-2/neu. The studies summarized in this review showed that serial changes in Serum HER-2/neu levels consistently paralleled the clinical course of metastatic breast cancer and provide a new tool for managing patients with HER-2/neu-positive breast cancer.



HER-2 status is an important biomarker in guiding personalized HER-2 therapy

Carney, WP. Personalized Medicine 2005;2(4): 317-324.

Among this review's conclusions: Identifying the HER-2/neu status of a patient is essential for guiding trastuzumab therapy; tissue tests indicate that 20-30 percent of patients with primary breast cancer have HER-2/neu-positive tumors, whereas an average 45 percent (23-80 percent) of metastatic breast cancer patients presented with HER-2-positive tumors by measuring HER-2/neu in their serum. However, evidence presented in this report shows HER-2/neu

tissue status can differ based on the test methods used at the time of HER-2/neu assessment. For instance, the HER-2/neu status of the primary breast cancer is used to determine if a patient will receive trastuzumab during MBC. However, not all HER-2/neu test results from the primary breast cancer are correct, which means there is a population of patients designated HER-2/neu negative by tissue tests that have HER-2/neu-positive tumors. This observation has important therapeutic implications for breast cancer patients with HER-2/neu-positive tumors who are not eligible for anti-HER-2/neu therapy.