Submission to Include the serum HER-2 Blood Test into Breast Cancer Guidelines.

Currently the standard of care for women with breast cancer is to establish the HER-2 status of the primary tumor using either an IHC or FISH test. However, once the tumor is removed there is only one practical way to routinely monitor for HER-2 status and that is with a HER-2 blood test. The HER-2 protein is a full-length glycoprotein with a 97-115 kDa extracellular domain (ECD) and well documented to be released into circulation. It can be accurately and reproducibly quantitated in the serum component of blood in both normal individuals and breast cancer patients. The serum HER-2 (sHER-2) test is FDA cleared (K994112, K024017) and measures the level of the ECD with 2 monoclonal antibodies directed to epitopes on the ECD that capture and quantitate circulating HER-2 levels in serum using an immunoassay format (1-33). Numerous clinical studies demonstrate that monitoring changes (increases or decreases) in sHER-2 levels in MBC patients can be an early indicator of cancer progression, response to therapy, parallels clinical status or predicts therapy resistance (3-33). In fact, several studies have reported that increasing sHER-2 levels can precede progression by up to 2 years prior to clinical symptoms and best exemplified by Sorensen et al. (20,25). Clinical studies have shown that a normal sHER-2 level is < 15 ng/mL, while an elevated (above normal) level is 15 ng/mL or greater (K994112,). The prevalence of elevated sHER-2 levels greater than 15 ng/mL ranges from 5–23% in early breast cancer (27-29) and as high as 90% in HER-2 tissue positive MBC patients (9,16). An increase or decrease of 20% or more from one patient blood draw to another has been established as a significant change in the HER-2 level (K994112, 2). Several studies have shown that an increase of 20% or more reflects disease progression while decreases of greater than 20% reflect therapy response or stable disease. In a recent report by Petersen et al. (26), 48 HER-2 tissue positive patients treated with Trastuzumab for up to six years or until death were monitored with the sHER-2 test. A significant decrease in sHER-2 of ≥20% correlated with no disease progression in 20 out of 21 clinical courses while a significant increase in serum HER-2 of ≥20% correlated with disease progression in the disease in 40 out of 44 clinical courses. Patients with no recurrence after Trastuzumab treatment had a median sHER-2 concentration of 10.5 ng/ml, whereas patients alive with recurrence had a median sHER-2 of 20.1 ng/ml (p=0.002). Patients who died due to recurrence had a median sHER-2 of 232.4 ng/ml at the latest measurement before death, (p=<0.0000001) compared to patients without recurrence (26). A decrease in sHER-2 levels greater than 20% at a median of 30 days from pre-treatment samples in anti-HER-2 therapy treated patients was strongly associated with progression free survival (7, 17, 22). In contrast, increases in sHER-2 levels greater than 20% from visit to visit, persistently high levels or failure to achieve at least a 20% drop in early weeks of anti-HER-2 therapy is strongly associated with shorter progression free survival (2,3, 6, 8,12,17,18,22). Patients with

sHER-2 levels that are consistently less than the normal 15ng/ml have significantly longer survival than patients with sHER-2 levels continuously greater than 15ng/ml (8,12,18). In a meta-analysis of 4030 breast cancer patients with either early stage or late stage disease, patients with sHER-2 levels > 15ng/ml had a 3.39-4.57 odds of recurrence within 2 years than patients with sHER-2 levels < 15ng/ml (30). This meta-analysis was strongly supported by a publication in 2013 by the clinical group led by Dr Edith Perez (32) and previous reports Dr Schippinger (8) and Dr Hayes (31). Numerous studies have shown that the sHER-2 test specifically measures levels of the HER-2 ECD and that the level is independent of therapy type and the test is not restricted to those receiving HER-2 targeted therapies (3,7,8,10-19).

Many reports have also documented that there is a significant number of breast cancer patients with a primary breast tumor that was classified as HER-2 negative but who develop a recurrent HER-2 tissue positive metastatic tumor (33-46) The evidence to support this observation has been demonstrated in 3 ways. A comparison of the primary tumor with the metastatic tumor from the same patient using IHC and FISH tests has revealed there are a significant number of breast cancer patients that can have a HER-2 negative primary tumor but a corresponding HER-2 positive metastatic tumor (34-40). Similarly, it has been shown that women with a HER-2 negative primary tumor can have HER-2 positive circulating tumor cells in the metastatic setting (41-43). Thirdly it has been shown repeatedly, that women with a HER-2 negative primary tumor can have elevated serum HER-2 levels (>15ng/ml) with the development of metastatic cancer (2, 9,11,13,17,18,20,23,25,33,38,42,44-46). Ardavanis et al., (44) reported that in a population of patients that were HER-2 negative by tissue testing but who received Trastuzumab therapy based on an elevated serum HER-2 level, that 73% of the patients derived clinical benefit. Since selection for HER-2 targeted therapies is based on the IHC/FISH results of the primary tumor there is a significant population of women who may be missing an opportunity to be treated with approved HER-2 targeted therapies or missing the opportunity to participate in clinical trials with new HER-2 targeted therapies. Therefore, the presence of elevated sHER-2 levels or increasing sHER-2 levels may be an additional aid in identifying those MBC patients incorrectly classified as HER-2 negative. Several authors (20,25,33,44) have pointed out that routine testing for elevated sHER-2 levels can complement HER-2 tissue testing and provide valuable information for patient management in both the HER-2 positive and HER-2 negative breast cancer patients which was reviewed in reference 46. Reference 46, only included publications that used the standardized FDA cleared serum HER-2 test .

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