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HER2 protein expression predicts response to trastuzumab in FISH-positive patients

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Background: Fluorescent in Situ Hybridization (FISH) is currently employed to select patients for trastuzumab or lapatinib therapy. However, only a portion of patients will respond to these HER2-directed therapies. Using a novel assay to quantitate total HER2 (H2T) and HER2 homodimer (H2D) levels, we examined the relationship between these measurements and clinical outcomes in a cohort of trastuzumab-treated metastatic breast cancer patients previously assessed as FISH positive by central testing.

Methods: The VeraTag assay was used to measure H2T and H2D. A cutoff previously defined by positional scanning was used to classify patients as H2T high or low (Leitzel et al. ASCO abstract # 1002, 2008). FISH status was determined using the Vysis assay and was performed by a single pathologist under standardized conditions (central testing). FISH + was defined as HER2/CEP17 ratio greater than 2.2. Kaplan-Meier and Cox proportional hazards analyses (TTP and OS) were conducted.

Results: 99 MBC patients previously scored as IHC 3+ or 2+, FISH+ and treated with first line trastuzumab-containing regimens were re-tested by central FISH. 22 patients were found to be FISH- and 77 were FISH+. 67 FISH+ patients had high H2T levels, and 19 FISH- patients were H2T low. 14% (3/22) of FISH- patients were H2T high, and 13% (10/77) of FISH+ patients were H2T low (overall discordance rate = 13%). In Kaplan Meier analyses, patients assessed as FISH+, H2T high had a significantly longer TTP (median TTP=11.3 mos.) compared to those who were FISH-, H2T low (median TTP=4.5 mos. HR=0.42, p=0.0006), and also compared to those who were FISH+, H2T low (median TTP=3.7 mos. HR=0.43, p=0.01). Those patients who had discordant results (FISH+, but H2T low) behaved similarly compared with FISH-, H2T low (HR=1, p=0.99). Similar results were observed using H2D. In analyses restricted to central FISH+ patients only (N=77), Cox proportional hazards multivariate regression identified H2T as an independent predictor of TTP (HR=0.29, p=0.0015) and OS (HR=0.37, p=0.02).

Conclusion: In metastatic breast cancer patients previously assessed as FISH-positive by central testing, we observed an approximate 55-fold distribution of HER2 protein expression. Patients with HER2 gene amplification by FISH but low HER2 total protein expression or homodimer levels as measured by the VeraTag assay respond poorly to trastuzumab-containing therapy.

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