

**HER2 expression and HER2-HER2 dimerization identifies subpopulations of metastatic breast cancer patients with different probabilities of long-term survival following trastuzumab treatment and with different requirements for concomitant chemotherapy.**

Michael Bates<sup>1</sup>, Christine Desmedt<sup>2</sup>, Jeff Sperinde<sup>1</sup>, Weidong Huang<sup>1</sup>, Denis Larismont<sup>2</sup>, Virginie Durbecq<sup>2</sup>, John Winslow<sup>1</sup>, Colombe Chappey<sup>1</sup>, Martine Piccart<sup>2</sup> and Christos Sotiriou<sup>2</sup>

<sup>1</sup>Monogram Biosciences, Inc., South San Francisco, CA, USA

<sup>2</sup>Jules Bordet Institute, Brussels, Belgium

**Background:** Selection of patients for treatment with trastuzumab is currently based on the semi-quantitative measurements of HER2 protein expression (IHC) or gene amplification (FISH). We made quantitative measurements of HER2 expression and homodimerization using a novel eTag assay technology, and correlated them with survival and time-to-progression (TTP) following trastuzumab treatment in a cohort of patients with metastatic breast cancer (MBC). We also examined the benefit of concomitant chemotherapy (CT) depending on quantitative HER2 expression.

**Methods:** The Jules Bordet cohort (Brussels, Belgium, N=71) had MBC and prior treatment with at least two CT regimens. Patients received trastuzumab alone or combined with paclitaxel. Independent medical data review and central confirmation of HER2 over expression by FISH (N=64) or IHC (N=7) were mandatory. The eTag assay was used to quantitate HER2 protein expression and HER2-HER2 dimers in FFPE specimens. eTag measurements were correlated with overall survival and TTP using Kaplan-Meier and Cox Proportional Hazards regression analyses.

**Results:** Cox analyses identified three independent correlates of survival and TTP; number of metastatic sites (HR for death = 2.4/site 95 % CI 1.5-3.8,  $p = 0.00019$ ), treatment with trastuzumab only (HR for death = 3.5, 95 % CI 1.3-9.6,  $P = 0.036$ ) and HER2 expression level (HR for death = 0.24/log10 (HER2), 95% CI 0.09-0.7  $p = 0.0058$ ). Patients with higher HER2 expression (above the median) experienced better overall survival than the lower half (HR 0.24,  $p = 0.0014$ ). Patients above the median of HER2 expression did not benefit from added CT (HR = 0.95,  $p = 0.94$ ), while patients in the lower half of the HER2 distribution did (trastuzumab alone HR 4.4,  $p = 0.018$ ).

**Conclusion:** Within a population of patients selected by FISH or IHC to receive trastuzumab, higher HER2 expression correlated with better outcomes. Patients with high HER2 expression derived no benefit from concomitant chemotherapy while patients with low HER2 expression benefited significantly from the addition of CT to trastuzumab.