Methods: Expression of 55 BC-related genes was determined by nCounter in tumor samples from a retrospective series of 58 T-DM1-treated patients (pts) with advanced BC from two independent institutions. Genes associated with T-DM1 overall response (OR; partial or complete) were identified using two-class unpaired SAM. Cutoff Finder (Plos One 2012) was used to optimize cutoff to predict OR. Uni- and multi-variate analysis for OR were performed using logistic regression. Nine BC cell lines (4 HER2-) were treated with T-DM1 (1.25 μg/ml) for 72 hours; treatment response (reduction in cell viability) was correlated to ERBB2 levels. Finally, % of ERBB2-high tumors across HER2 IHC groups was explored in 392 and 368 primary BCs from an in-house (nCounter) and the TCGA (RNAseq) datasets, respectively.

Results: HER2 IHC status in T-DM1-treated pts was: IHC0 (n = 5), IHC+1 (n = 3), IHC+2 (n = 12), IHC+3 (n = 35). 60% of pts were HR+, 72% received 1 prior line of trastuzumab and 93% had visceral metastases. OR rate was 43%, median PFS was 5.3 months (95% CI 3.9-7.6). GRB7 and ERBB2 were the top 2 genes associated with OR (FDR<1%). Although HER2 IHC (3+ vs ≤ 2+) was associated with OR in univariate analysis (p = 0.027), only ERBB2 expression (ORR 1.93, p = 0.021) and number of prior therapy lines (0-1 vs ≥ 2) were independently associated with OR. An ERBB2 cut-off was optimized to predict OR (100% sensitivity, 36.4% specificity, AUC 0.69). In BC cell lines, the ERBB2 cutoff predicted T-DM1 activity (median cell viability 43% vs. 100%, p = 0.015). Importantly, T-DM1 response across BC cell lines strongly correlated with ERBB2 continuous expression (r = 0.88). Finally, ERBB2-high distribution within HER2 IHC groups in both datasets (in-house and TCGA) was: 0% and 0% (IHC0), 1.10% and 0.59% (IHC+1), 0% and 0% (IHC+2/non-amplified), 9.38% and 25% (IHC+2/amplified) and 76.68% and 79.63 (IHC+3).

Conclusions: ERBB2 expression is associated with T-DM1 efficacy in BC regardless of HER2 IHC status. Lower ERBB2 cutoffs might be needed for highly potent anti-HER2 ADCs such as DS-8201.

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20P ERBB2 mRNA as predictor of response to anti-HER2 antibody-drug conjugates (ADC) in breast cancer (BC)

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Background: Quantitative measurements of HER2 might identify the probability to respond to anti-HER2 ADCs better than semi-quantitative methods such as immunohistochemistry (IHC).