

26th EORTC-NCI-AACR SYMPOSIUM

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Presentation at the 26th EORTC-NCI-ACR symposium on "Molecular targets and Cancer therapeutics", in Barcelona, 18-21 November 2014

Her2-3 heterodimers is a new and better then HER2 IHC score for clinical outcome prognosis.

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The efficacy of anti-Her2 therapies in Her2-positive breast cancer patients is proven and well documented. However, some patients with Her2-negative tumours also benefit from the same therapies (NSABP B-31) and there is no solid hypothesis to explain those observations. Furthermore, the definition of positive vs. negative Her2 status actually reflects overexpression of Her2 above levels detected in normal and non-malignant tissues. Her2 can heterodimerize with other members of the EGFR family, regardless of expression levels, but the dimerization is dependent upon availability of ligand(s). Her2-Her3 dimer has been shown to drive proliferation of breast cancer cells. We have developed a new FRET/FLIM (Förster resonance energy transfer/fluorescence-lifetime imaging microscopy) based assay reporting protein-protein interaction at distance below 10 nm for detection of Her2-Her3 dimer in formalin-fixed paraffin embedded (FFPE) patient samples. Fluorophore labelled antibodies against Her2 and Her3 allow us to measure a FRET signal, which is dependent upon the number of interacting molecules. Using FFPE samples from the METABRIC cohort, we found that the interaction between two proteins does not correlate with expression levels of interacting partners as judged using standard IHC scoring system. The FRET signal measurements were evenly distributed across all samples with 0, 1, 2 and 3-plus scores for Her2 expression. Mathematical modelling suggests that the absence of correlation between Her2 and Her3 protein and their dimer levels, although can be quite unintuitive, is in principle possible, particularly under scenarios when both Her2 and Her3 compete for binding with other receptor tyrosine kinases including the other ErbB family receptors. Interestingly, we also did not find any correlation with known genetic signatures associated with cancer progression. However, a low FRET signal significantly correlated with longer metastasis free survival, when patients with metastatic events up to 10 years are considered. Our findings may pave the way for better understanding of the biology of EGFR family receptor's adaptation to drug treatment, helping to predict individual patient response to select the right patient for appropriate treatment.