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genomics and proteomic analysis of breast cancer

24P Phosphoproteomic assessment of HER2 signaling pathway in HER2 non-amplified patients of the GeparQuattro and GeparQuinto trials

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The benefit of anti-HER2 treatment in combination with chemotherapy may not be limited to patients with HER2 amplification. This study tested if phosphorylated HER2 (pHER2) and co-activation of downstream targets are predictive of response to anti-HER2 treatment in HER2 non-amplified patients. Patients classified as HER2 positive (IHC, FISH) by local testing from GeparQuattro and GeparQuinto trials received neoadjuvant anti-HER2 treatment (trastuzumab or lapatinib) in combination with anthracycline-taxane-based chemotherapy. On central pathology review 98 out of 1060 patients were HER2 non-amplified. In order to assess the potential benefit from anti-HER2 treatment in these patients the levels of pHER2 and downstream targets including pHER3, EGFR, AKT, PI3K, ERK, PTEN, S6RP and phosphorylated forms were quantitatively assessed using reverse-phase protein arrays. Histopathological complete response (pCR; ypT0/is) and disease free and overall survival served as reference standard. 25 (26%) patients achieved pCR. The level of pHER2 was not significantly different between groups of histopathologic responders and non-responders. S6RP and pS6RP were the only proteins significantly associated with pCR ($p = 0.01$ and 0.03) with a higher pretherapeutic expression in patients who achieved pCR. Low expression of S6RP and pS6RP were associated with longer disease free ($p < 0.01$) and overall survival ($p < 0.05$). Expression of S6RP and pS6RP did not correlate with other HER2 signaling proteins, whereas all remaining proteins were positively correlated with each other. Expression of S6 ribosomal protein (S6RP), a downstream target of S6 kinase, and pS6RP are significantly associated with short and long-term outcome following anti-HER2 treatment in HER2 non-amplified breast cancer patients. In contrast, activation status of the HER2 pathway reflected by pHER2 and other downstream targets was not predictive of response, and showed no significant correlation with S6RP expression. This suggests S6RP and pS6RP as novel predictive biomarkers for response to anti-HER2 treatment in non-amplified patients, possibly through a mechanism independent of global HER2 pathway activation.

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