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The EGFR-family member HER2 drives cancers in various organs and organ systems, especially in the breast and lung. For solid tumors that overexpress HER2 (HER2+), targeted therapies include antibodies such as trastuzumab and, more recently, small molecules inhibitors. However, relapse and progression have been observed in a significant fraction of cases, suggesting the presence of mechanisms of resistance. Our lab previously identified somatic HER2 mutations in breast cancers that conferred resistance to small molecule HER2 inhibitors, and based on patient data from a clinical trial, we speculated that 776insYVMA and 780insGSP (henceforth referred to as YVMA and GSP, respectively), two insertion mutations commonly found in lung adenocarcinomas, might confer similar resistances as well.

To test this possibility, we examined the effect of three small molecule tyrosine-kinase inhibitors (lapatinib, neratinib, and afatinib) on the cell growth and signaling of HER2-negative MCF10A cells transduced with wildtype HER2, HER2 YVMA, or HER2 GSP. Each tyrosine kinase inhibitor (TKI) was introduced into the in-vitro cell media at a range of concentrations, in order to construct a dose-response curve. Cell growth was measured via the Alamar Blue assay, while Western blots were used to detect the quantity of phosphorylated and total HER2, MAPK, and AKT.

We found that YVMA was a potent resistance mutation. Compared with HER2 WT transduced cells and vehicle control, HER2 YVMA conferred near-total resistance to lapatinib and strong resistance to neratinib and afatinib, in both cell growth and cell signaling. HER2 GSP seemed to be a more modest resistance mutation, conferring total resistance to lapatinib but only moderate resistance to neratinib and afatinib. These data are consistent with previously observed clinical outcomes for patients with these mutations, and imply that the HER2 YVMA and, to a lesser degree, HER2 GSP mutations are responsible for a portion of the poor clinical responses to lapatinib and afatinib in breast and lung cancer patients.