

STRATEGIES TO OPTIMISE ANTI-RECEPTOR THERAPIES

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Anti-epidermal growth factor receptor (EGFR) agents including monoclonal antibodies (Mabs) and tyrosine kinase inhibitors have clear, but modest, single-agent antitumor activity in epithelial tumors. A strategy to augment their activity would be to treat tumors that depend on the EGFR pathway. Early data from anti-EGFR Mabs clinical trials have shown that, unlike with anti-erbB2 therapies, higher levels of EGFR expression by immunohistochemistry (IHC) do not predict higher response rates. Therefore, a comprehensive evaluation of EGFR regulating and dependent genes may be required. We are performing pre and post treatment IHC assays to study tumor expression of EGFR ligands and activated EGFR, ERK, PI3K and Akt. The recently reported ability to profile gene expression using fixed paraffin-embedded tissues (FPET) could enable development of new molecular assays to guide selection of patients for anti-EGFR (and other targeted) therapies. We are collaborating with scientists at Genomic Health, Inc. who have developed new validated assays that can quantitate gene expression of up to 400 cancer-related genes from archival tumor blocks. We are exploring in head and neck carcinoma, colon carcinoma, and breast carcinoma the correlation between molecular profiles and other assessments, such as activation of the ERK's by IHC and clinical response to EGFR inhibitor therapy. Archival tumor tissue from 75 patients, including patients treated with anti-EGFR agents, are being assayed for quantitative expression of the HER kinase system, and for more than 160 other genes important in growth, proliferation, signaling, and apoptosis. The following HER kinase system genes are assayed: EGFR, ErbB2, ErbB3, ErbB4, TGFalpha, Amphiregulin, Beta-cellulin, HB-EGF, MMP9, Erk1, Erk2, STAT1, STAT3, STAT5A, and STAT5B. Initial data on 19 patients with head and neck cancer showed that EGFR and TGFalpha genes were expressed in the tumor tissue in all patients. Of note, there was a large variation in EGFR expression between patients (up to 100-fold) and a smaller variation in TGFalpha expression between patients (up to 15-fold). We will present and discuss the data we have obtained on the correlation between quantitative gene expression and IHC expression. The results from this study will be used to design larger studies required to confirm the clinical utility of these new FPET tumor assays to guide the selection of patients for EGFR-targeted therapy.