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Targeting the epidermal growth factor receptor family

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The epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase of the ErbB family that is abnormally activated in many epithelial tumors. Several mechanisms lead to the receptor's aberrant activation that is observed in cancer and two classes of anti-EGFR agents are currently approved for the treatment of patients with cancer: Monoclonal antibodies directed at the extracellular domain of the receptor, and low molecular weight (MW), ATP-competitive inhibitors of the receptor's tyrosine kinase.

Anti-EGFR monoclonal antibodies are active in advanced colorectal carcinoma and in a variety of epithelial tumor types including head and neck cancer and non-small cell lung cancer (NSCLC). The development of low MW, anti-EGFR tyrosine kinase inhibitors (TKIs) has been focused on NSCLC although responses have been reported for other types of cancer. One of these agents, erlotinib, has been approved based on demonstrating improved survival in patients with advanced NSCLC that previously had been treated with chemotherapy.

Recently, the discovery of EGFR somatic mutations in NSCLC has resulted in important implications for the biology, treatment, clinical trial design and methods for mutation detection. These mutations occur in exons 18 through 21 encoding the TK domain of the EGFR and there is a close association between these mutations and responses to EGFR TKIs. There is evidence, however, that the clinical benefit observed with anti-EGFR TKIs is not restricted to those patients harboring *EGFR* gene mutations. The response rate to treatment with EGFR TKIs has also been reported to be higher in patients with polyploidy or amplification of the EGFR gene. On the other hand, it is likely that other mutations in other genes may play a role in sensitivity or resistance to inhibitors of EGFR, due to dependence of the receptor's biologic activity on activated downstream signaling pathways. This can be exemplified by the potential resistance to these agents in patients harboring *KRAS* or phosphatidylinositol-3 kinase (*PI3K*) mutations. In the case of tumors with *PI3K* mutations, they may be PI3K signaling-dependent and might be highly sensitive to inhibitors of the PI3K/Akt/mTOR pathway. We are studying, therefore, combined approaches of anti-EGFR therapy and mTOR inhibitors. In addition, other strategies are attempting to identify molecular markers that can predict patients more likely to respond to anti-EGFR therapy. We have taken an approach to conduct a series of clinical studies with on-study tumor biopsies trying to identify those patients that respond to EGFR antagonists. In an pilot study with erlotinib in NSCLC, early on-study tumor apoptosis correlates with clinical benefit. These findings are being confirmed in a larger multicentric trial.

In addition to "pure" EGFR inhibitors, there are available low MW TKIs that target both the EGFR and other members ot the erbB family. Lapatinib, a dual inhibitor of the EGFR and HER2, has showed clinical activity in patients with trastuzumab-refractory breast cancer and a high response rate in the first line setting. Clinical development is ongoing with other dual EGFR-HER2 TKI's such as BMS-599626 and AEE788. It is possible that these dual inhibitors may have activity in a subgroup of tumors that overexpress a truncated version of the HER2 receptor that lacks the extracellular domain.

In summary, EGFR targeting has demonstrated to be a fruitful approach to anticancer therapy resulting in improved survival in a variety of epithelial tumors. Ongoing efforts are being directed at the integration of this form of therapy to conventional agents, and identifying the optimal clinical scenarios for their application and at the identification of tumors "EGFR dependent".