EGFR Genomic Testing in Non-Small Cell Lung Cancer

Epidermal growth factor receptor (*EGFR*) is a protein kinase involved in key cellular processes that include growth, differentiation, apoptosis, and morphogenesis. It is commonly overexpressed on the surface of cells in a variety of human epithelial cancers, including NSCLC. Mutations in the *EGFR* gene within tumor tissue have been explored as predictive markers of response to the small-molecule tyrosine kinase inhibitors (TKI) erlotinib (Tarceva®) and gefitinib (Iressa®). The goal of *EGFR* mutation testing in this setting is to identify patients with "activating" mutations in the EGFR gene, who are most likely to benefit from targeted therapy with these agents and thus candidates for their use.

Evidence – A 2011 systematic review states that current evidence is consistent in suggesting that patients with EGFR-positive tumors are likely to respond favorably to TKIs, while patients with wild-type tumors are not and should be offered alternatives. Importantly, responders to TKIs, especially erlotinib, fair better than those treated with conventional chemotherapeutic agents.[1] Concurrent evidence, albeit less mature, suggests that other biomarkers, including molecular (e.g., KRAS, ALK), may contribute to even better stratification of these patients.

National Comprehensive Cancer Network (NCCN) Guidelines, version 1.2011, for the treatment of NSCLC (2010) includes a category 1 recommendation for EGFR testing for the following NSCLC histologies: adenocarcinoma, large cell, and NSCLC not otherwise specified. NCCN concluded that EGFR testing is not recommended for squamous cell carcinoma of the lung.[2]

American Society of Clinical Oncology (ASCO) published a guideline update on chemotherapy for stage IV NSCLC. This guideline includes an updated recommendation that first-line use of gefitinib may be considered for individuals with a known activating EGFR tumor mutation, but for negative or unknown EGFR mutation status, cytotoxic chemotherapy is still preferred.[3]

***EGFR* testing** – A variety of molecular testing methods have been developed to measure the presence of mutations to the *EGFR* gene, which include mutation analysis, copy number changes (i.e., duplication or deletion), and immunostaining of the *EGFR* protein itself. It is the subset of *EGFR* mutations in exons 19 (deletion) and 21 (point mutation) that are the most reliable indicators of a positive response, considered "activating" mutations. Neither EGFR protein expression by immuno-staining nor gene copy number by FISH is a reliable biomarker for this purpose. Testing is available from ARUP Labs and others, and testing should be performed only by laboratories with demonstrated proficiency.

Recommendation: Prior to initiating treatment with tyrosine kinase inhibitors in advanced NSCLC, *EGFR* testing of tumor mutation status (that includes exons 19 and 20) should be performed.

Key Resources:

1. BCBS Technology Evaluation Center. Epidermal growth factor receptor mutations and tyrosine kinase inhibitor therapy in advanced non-small cell lung cancer. 2011(March):1-5. http://www.bcbs.com/blueresources/tec/vols/25/25_06.pdf.
2. NCCN. Non-Small Cell Lung Cancer. *Practice Guidelines in Oncology.* 2010. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.
3. Azzoli CG, Baker S, Jr., Temin S, et al. American Society of Clinical Oncology Clinical Practice Guideline update on chemotherapy for stage IV non-small-cell lung cancer. *J Clin Oncol.* Dec 20 2009;27(36):6251-6266. http://www.guideline.gov/content.aspx?id=15478.