HPV and EGFR Signaling

- Keratinocyte cell lines generated by co-transfection with HPV-16 E6 and E7 show upregulation of EGFR (Welling, 1996)
- p53 transactivates EGFR in E6 dependent manner (Deb, 1994)
- E5 protein mediates oncogenic effects in part via EGFR (Tsuji, 2003)
- Activates EGFR-induced proliferation
  - Inhibits tumor suppressor p51

HPV-Associated Proteins

- E1: DNA replication
- E2: Regulates E6, E7 expression
- E4: Disrupts cytokeratin network
- E5: via EGFR as above
- E6: Transformation via binding to p53, telomerase activation
- E7: Transformation via binding to p18

Abstract

- Background: Epidermal growth factor receptor (EGFR) expression and HPV infection are common in SCAC. We therefore initiated 2 phase II studies to evaluate the safety and efficacy of the EGFR inhibitor Cetuximab (CX) given concurrently with CDDP/5-FU/RT in HIV-positive (AMC045) and immunocompetent (E3205) patients with SCAC.

- Methods: All patients received CX (400 mg/m2 loading, then 250 mg/m2 IV q 2 weeks) plus CDDP (75 mg/m2 IV q 4 weeks) and 5-FU (1000 mg/m2 IV q 4 weeks) infusions days 1-4 (grade 4 RT skin, diarrhea) or II (grade 4 RT skin, diarrhea) adverse events, with prespecified rates (alpha=0.10, beta=0.10), the primary end point. Other endpoints included progression free survival (PFS) and overall survival (OS). The results below include complete toxicity and preliminary efficacy data (including only the first 28 patients from E3205).

- Results: Expressed reporting was required for type I (any grade 3-4) or II (grade 4 RT skin, diarrhea) adverse events, with prespecified rates of ≤5% or >20%, respectively defined as unacceptable. Early stopping rules were not invoked for either trial. LRF rates data will be presented after more detailed case review is completed (UPDATED 05/25/12).

- Conclusions: CX plus CDDP/5-FU/RT is feasible in patients with SCAC, including patients with HIV infection. Preliminary safety and efficacy data appear encouraging, but accrual without neoadjuvant CDDP/5-FU continues in E3205, and additional followup of both study cohorts is required in order to determine whether pre-specified efficacy endpoints were met.