Targeted therapy against VEGFR and/or EGFR signaling with AZD2171, vandetanib, and gefitinib as part of a combined modality approach for the treatment of non-small-cell lung cancer

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Background: The current challenge in NSCLC is to optimize available therapeutic strategies by incorporating new agents into existing treatment regimens. Strategies that target key signaling pathways offer great potential and two validated therapeutic targets are VEGF and EGF and their receptors. To study the potential therapeutic efficacy of lung cancer treatments we have developed orthotopic lung adenocarcinoma models that mimic clinical patterns of NSCLC growth, which are sensitive (H441) or highly resistant (PC14) to EGFR inhibition. EGFR is expressed in both models, though EGFR ligand expression (TGF-α/EGF) was observed only for the H441 lung adenocarcinomas and was associated with resultant endothelial expression and activation of EGFR.

Methods: Human lung adenocarcinoma cells (PC14 or H441) were injected into the left lungs of nude mice with lung tumors evident within 14 days. Tumor-bearing mice (10/group) were treated with (A) AZD2171 (RECENTIN™), a highly potent and selective inhibitor of VEGFR-1, -2, and -3 (6 mg/kg/day orally); (B) vandetanib (ZACTIMA™), a selective inhibitor of VEGFR-2 and EGFR (25 mg/kg/day orally); (C) AZD2171 plus paclitaxel (200 µg/week ip); (D) vandetanib plus paclitaxel; (E) gefitinib (IRESSA™), a highly selective inhibitor of EGFR (25 or 75 mg/kg/day orally); (F) gefitinib plus paclitaxel. H441 tumors, but not PC14 tumors, were sensitive to EGFR inhibition, and was associated with resultant endothelial expression and activation of EGFR.

Results: Vandetanib or AZD2171 treatment substantially reduced lung tumor burden in both the H441 and PC14 tumor models, and prevented mediastinal adenopathy and pleural effusion relative to controls. In both models, the antitumor and antimetastatic effects of AZD2171 and vandetanib were markedly enhanced when they were combined with paclitaxel. Immunohistochemical analyses of H441 lung adenocarcinoma revealed that tumor and endothelial cell VEGFR activation was inhibited by vandetanib or AZD2171 therapy alone and in combination with paclitaxel in lung tumors. Vandetanib or AZD2171 inhibited tumor angiogenesis and enhanced the antivascular and antitumor effects of paclitaxel. H441 tumors, but not PC14 tumors, were sensitive to EGFR signaling inhibition by gefitinib, which enhanced the antitumor and antivascular effects of AZD2171 in a dose-dependent fashion for H441 lung adenocarcinomas. Immunohistochemical evaluation of H441 lung adenocarcinomas showed that angiogenesis, tumor cell proliferation, and expression of proangiogenic and invasive molecules were substantially reduced by treatment with AZD2171 in combination with gefitinib compared with either agent alone.

Conclusions: These studies demonstrate that VEGFR signaling inhibition by AZD2171 or vandetanib inhibits tumor growth and angiogenesis in orthotopic human lung adenocarcinoma models. The antitumor and antivascular effects of AZD2171 or vandetanib were substantially enhanced when they were combined with paclitaxel. EGFR signaling inhibition enhanced the therapeutic efficacy of VEGFR signaling inhibition for H441 lung tumors, which express both EGFR and its ligand(s). These findings provide mechanistic insights into the biology underlying the beneficial combination of AZD2171 or vandetanib with paclitaxel in lung cancer, and suggest that a customized approach for combined EGFR and VEGFR signaling inhibition based upon EGFR expression and activation in lung tumors and endothelial cells warrants further investigation.

Correlative study of EGFR mutations or protein expressions of EGFR, phosphorylated HER2, phosphoHER2 and IGF-R1 with gefitinib sensitivity in patients with non-small cell lung cancer: Results of West Japan Thoracic Oncology Group trial (WJTOG0203A)

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Background: Both epidermal growth factor receptor (EGFR) mutation and gene copy number of HER2, a member of EGFR family, are associated with gefitinib sensitivity. We carried out a correlative study to determine the relationships between EGFR mutations, EGFR or HER2 protein expressions, their activation status (pEGFR, pHER2) or insulin-like growth factor receptor 1 (IGF-R1) protein expressions and clinical outcomes after gefitinib treatment in advanced NSCLC.

Method: Tumors from patients (pts) were evaluated for EGFR mutations by DNA sequence, and for protein expressions of EGFR, pEGFR, HER2, pHER2 and IGF-R1 by immunohistochemistry. Time to progression (TTP) was calculated by the Kaplan-Meier method; groups were compared using the log-rank test. Risk factors associated with TTP were evaluated with Cox proportional hazard regression modeling. Correlation between EGFR mutation and response was evaluated by Fisher’s direct method. Relationship between each protein expression and response was tested by two-sided. Primary endpoint was to detect biomarkers to predict gefitinib sensitivity.

Results: From Dec. 2003 to Dec. 2005, 103 consecutive pts were enrolled onto the study, and received gefitinib until disease progression. Median age was 68 years, female (58%), adenocarcinoma (83%), never smoker (55%) and no previous chemotherapy (49%). 98 pts were evaluable for efficacies, toxicities and gene analyses. Forty-one pts (42%) had EGFR mutations; 14 pts had deletion mutation in exon 19, 27 pts had missense mutation (L858R) in exon 21. EGFR mutations were significantly related to response (62 vs. 26%; P = 0.001), disease control rate (92 vs. 65%; P = 0.003) and TTP (median, 10.1 vs. 5.1 months; hazard ratio = 0.64; P = 0.048). Both pEGFR (0, +1 vs. 0}