Conclusion: The role of specific EGFR and KRAS genotype merits further continued investigation. As several trials of first-line gefitinib or erlotinib near completion, the ability to combine mutation data and clinical outcomes from increasing numbers of chemotherapy-naive patients in a web-based database may yield more powerful insight into roles of specific mutations and help guide treatment decisions. We anticipate the addition of a number of patients from Japan and from other trials in the coming months.

D2-07 Molecular Targeted Therapy: Biomarkers, Thu, 12:30 - 14:15

Mechanisms of activating PI3K signaling in lung cancers that become resistant EGFR tyrosine kinase inhibitors

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Background: Cancers that are sensitive to EGFR inhibitors down-regulate Phosphoinositid 3-Kinase (PI3K) signaling in response to these drugs. Inhibition of PI3K signaling appears to be critical for ErbB inhibitors to induce cell death. Although lung cancers with EGFR mutation often have initial impressive responses to EGFR inhibitors, they invariably develop resistance. In 50% of such patients, a single secondary mutation, a substitution of methionine for threonine at position 790 (T790M), has been identified. EGFR T790M is efficient to cause gefitinib resistance and leads to persistent ERBB3/PI3K/Akt signaling in the presence of gefitinib. However, the mechanisms by which the other half of cancers becomes resistant remain unidentified.

Methods: To identify novel mechanisms of resistance, we cultured highly sensitive EGFR mutant and amplified cell lines in the presence of increasing concentrations of gefitinib until resistant cell lines were produced.

Results: We found that, unlike the parental cells, all of the resistant cell lines maintain PI3K signaling in the presence of gefitinib. Some cell lines use ErBB3 (i.e., no change from the parental cell line), whereas others utilize new adaptor proteins. Blocking the new mechanisms of activating PI3K leads to cellular death in the resistant cell lines.

Conclusions: Cancers that become resistant to EGFR inhibitors acquire novel mechanisms for activating PI3K. Inhibiting these pathways may be effective methods for treating cancers with acquired resistance to EGFR inhibitors.
targeted prescription of chemotherapy with appropriate platinum combination.

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D3-02 Pharmacogenomics & Biomarker in Cytotoxic Chemotherapy, Thu, 12:30 - 14:15

Updated Paclitaxel-Carboplatin Pharmacogenomic (PG) Analysis of Japan-SWOG Common Arm Study in Advanced Non-Small Cell Lung Cancer (NSCLC)

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Background: Ethnic or racial differences in drug disposition (population-related pharmacogenomics) may explain conflicting results of clinical trials using similar treatment. We prospectively designed 3 separate phase III trials in advanced NSCLC (FACS & LC03 in Japan, S0003 in USA) with a paclitaxel-carboplatin “common arm” in order to compare outcomes. Differences in toxicity and efficacy were noted between the 2 Japanese studies and S0003 (Gandara, ASCO 05 & Crowley nationa 06). Without outcomes. Differences in toxicity and efficac

Methods: Genomic DNA was prospectively collected from patients (pts) in 2 of these Phase III trials (LC03 [N=78, 37 on common arm] & S0003 [N=78]) with identical eligibility, staging, treatment paclitaxel (225mg/m2) & carboplatin (AUC 6), response & toxicity criteria. We analyzed for genotypic variants related to paclitaxel or platinum by pyrosequencing, & assessed results by Cox model for survival/PFS & logistics regression for response/toxicity.

Results: We will present an updated PG analysis for additional genotypic variants. There was a significant difference between Japan & US pts in genotypes: CYP3A4*1b (p=0.01), CYP3A5*3c (p=0.03), ERCC2 k751q (p < .001), and CYP2C8 r139k (p=0.01). Genotypic correlations were observed between CYP3A4*1b for PFS (HR 2.75, 1.06-7.08, p=0.04) & ERCC2 k751q for response (HR 0.33, 0.13-0.84, p=0.02. For grade 4 neutropenia, the HR for ABCB1 3425c->T was 1.84 (0.77-4.48), p=19.

Conclusions: 1) Japanese and US pts in these studies differed in allelic distribution for genes involved in paclitaxel disposition or DNA repair. 2) Genotype-associated correlations were present for PFS (CYP3A4*1b) and response (ERCC2 k751q). 3) The small sample size limits interpretation of these data. 4) We will present plans for additional prospectively designed trials exploring population-related PGs based on this common arm model.

D3-03 Pharmacogenomics & Biomarker in Cytotoxic Chemotherapy, Thu, 12:30 - 14:15

IALT-Bio: a challenging research to improve adjuvant chemotherapy of completely resected NSCLC

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Background: The International Adjuvant Lung Cancer Trial (IALT) demonstrated that adjuvant cisplatin-based chemotherapy increases the 5-survival rate by absolute 4% in patients with completely resected NSCLC. Selection of those patients who benefit from chemotherapy would be of major clinical relevance. Clinical parameters such as age, gender or histology did not predict the benefit of chemotherapy. Thus we initiated a translational research project termed IALT-Bio. The aim of this project is to study molecular biomarkers of tumors for their potential predictive values with regard to the effect of adjuvant chemotherapy on survival in IALT patients.

Methods: Five groups of molecular biomarkers (19 markers in total) were studied: drug transporters, DNA repair, cell cycle regulators, signal transduction, apoptosis. Expression of biomarkers was determined by immunohistochemistry. Overall survival was analyzed with Cox models adjusted for clinical and pathological factors.

Results: Tumor specimens were collected from 867 patients from 28 IALT centers. These patients represented 46% of all IALT patients and 83% of the patients enrolled by the 28 centers. Collection of the tumor specimens of a world-wide clinical trial posed several problems including ethical and logistic problems. All tumor specimens were pathologically examined and 783 samples were considered to be of sufficient quality for further analyses. The laboratory analyses of the various biomarkers were performed by several research groups. ERCC1 expression was shown to be of prognostic and predictive value. Patients with ERCC1-negative tumors benefited (hazard ratio of death 0.65, 95% CI 0.5-0.86) from adjuvant chemotherapy, whereas no benefit (hazard ratio 1.14, 95% CI 0.84-1.55) was seen in patients with ERCC1-positive tumors (p value for the comparison of the two hazard ratios: 0.009) (Olaussen KA et al., NEJM 2006, 355, 983). Similarly, absence of p27 expression predicted benefit of adjuvant chemotherapy (Filipits M et al., JCO 2007, in press). The corresponding hazard ratios were 0.66 (95% CI 0.5-0.88) for patients with p27-negative tumors and 1.09 (95% CI 0.82-1.45) for those with p27-positive tumors, respectively (p value for the comparison of the two hazard ratios: 0.02). ERCC1 and p27 were predictive independently of each other. When ERCC1 and p27 were combined, the predictive values were further increased: the hazard ratios were 0.52 (95% CI 0.36-0.74) for patients with tumors negative for both biomarkers but 1.27 (95% CI 0.87-1.84) for those with tumors positive for both markers. These 2 groups comprised 58% of the patients. Multidrug resistance proteins (MRP1, MRP2) did not predict the outcome of adjuvant chemotherapy (Filipits M et al., manuscript submitted). Patients with FasL-negative tumors also benefit from adjuvant chemotherapy (Brambilla E et al., WCLC 2007). Analyses of other biomarkers including mutations of p53, k-ras and EGF receptor are still ongoing. Current research is attempting to validate these markers on patient populations from other adjuvant chemotherapy trials.

Conclusions: Both ERCC1 and p27 are of predictive value in patients with completely resected NSCLC undergoing adjuvant cisplatin-based...