of the acquired resistance while MET amplification is responsible for about 20%. Irreversible inhibitors including HKI-272 and PF-299804 can cause growth inhibition in NSCLC cell lines with both the resistance and sensitizing mutations, while gefitinib and erlotinib do not. HKI-272 and PF-299804 entered directed phase I and phase II trials in patients previously treated with gefitinib and erlotinib and mutation testing has been prospectively incorporated into the trials.

Conclusions: Biomarkers of response to EGFR-TKIs have been identified in retrospective studies of patients with non-small cell lung cancer and are now being prospectively incorporated into clinical trials of gefitinib and erlotinib. None of the biomarkers has yet been successful in these prospective trials to identify the subsets of patients who derive clinical benefit from the treatments but we await the results from additional ongoing clinical trials

S24
ERCC1 and response to chemotherapy

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Introduction: Today, cisplatin (and its analogs, carboplatin and oxaliplatin) remain the scaffolding of chemotherapy in many solid tumors including lung, head and neck, bladder, ovarian, and colon carcinomas. After several decades of clinical trials, a therapeutic plateau appears to have being reached with standard chemotherapy in most solid tumors. A re-evaluation of strategies to improve clinical outcomes is needed. At present, research in cancer survival is partly focused on translational pharmacogenetics, with the goal of providing individualized chemotherapy based on different genetic traits, such as polymorphisms, gene mutations, and overexpression of drug target gene transcripts. Also, in some instances, downregulation of crucial gene transcripts has been linked to enhanced chemotherapy response. At this time, one of the most relevant issues for cancer patients is the need for a reliable method to determine which chemotherapy combinations will have better chances of improving survival based on genetic markers. On that regard, defining the predictive and biological determinants of cisplatin response represent an important endeavor. The application of pharmacogenomics to cytotoxic chemotherapy could lead to the development of "individualized" drugs for patients with cancer. Numerous studies have reported the role of ERCC1 expression in the repair mechanism of cisplatin-induced DNA adducts in cancer.

Main Message: Numerous studies have reported the role of ERCC1 expression in the repair mechanism of cisplatin-induced DNA adducts in human ovarian cancer cells, in primary gastric tumors, in colorectal and esophageal cancer. ERCC1 expression has been negatively associated with response to cisplatin or oxaliplatin chemotherapy in gastric and colon cancer. High tumor tissue levels of ERCC1 mRNA in ovarian and gastric cancer patients have been associated with cisplatin resistance.

Taken altogether, these data suggest that ERCC1 is a potentially useful marker for predicting clinical resistance to cisplatin, carboplatin and oxaliplatin. Studies linking ERCC1 to resistance to platinum compounds have been conducted mainly by analysis of RNA or DNA. Nevertheless, recently ERCC1 protein expression was studied in resected NSCLC tumors from 761 patients from the International Adjuvant Lung Trial (IALT). Patients with ERCC1 negative tumors who were randomized to chemotherapy had significantly prolonged survival compared to those who were randomized to observation (test for interaction, $P < 0.009$; $HR = 0.65$; 95% CI [0.50−0.86]). In contrast, there was no survival difference between treated and none-treated patients among ERCC1 positive patients ($HR = 1.14$; 95% CI [0.84−1.55]). It was concluded that NSCLC patients with completely resected ERCC1 negative tumors seem to be stronger candidates for adjuvant cisplatin-based chemotherapy than those with resected ERCC1 positive tumors.

Conclusions: Based on these results, it is very probable that in the near future platinum-based chemotherapy could be chosen according to pharmacogenomic criteria such as ERCC1 expression on tumor tissue. Nevertheless, additional studies are warranted to standardize and optimize methodologies for ERCC1 analysis in tumor samples in order to define a biomarker profile predictive of patient outcome

S25
Gene signatures and response to chemotherapy in breast cancer: statistical artefact or reality?

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Introduction: Systemic chemotherapy for breast cancer improves overall survival, whether given pre-operatively or as post-operative adjuvant therapy. Newer chemotherapy regimens containing taxanes further improve survival compared to standard regimens but taxanes are expensive, toxic and may benefit only a small group of patients. Therefore, identification of regimen-specific predictive factors is a research priority.

Main Message: Several single arm neo-adjuvant chemotherapy trials have reported gene expression signatures obtained from tumour biopsies taken at diagnosis using conventional biostatistic methods (Chang et al. 2003, Ayers et al. 2004, Hannemann et al. 2005, Gianni et al. 2005, Hess et al. 2006, Cleator et al. 2006). Most of these studies reported signatures that predict clinical or pathological response. We will review briefly these studies and discuss their potential weaknesses.

Another approach is to use predictive signatures developed from cell lines (Potti et al. 2006). We used this approach to confirm the ability of these signatures to predict the response to chemotherapy of the ER negative breast tumours within a large series of patients enrolled in a recently completed phase III neoadjuvant trial (Bonnefoi et al. 2007). This sub-study was restricted to ER negative tumours because studies containing both ER positive and ER negative tumours are easily confounded by cell type bias linked to ER status. This trial compares a non-taxane regimen (fluorouracil + epirubicin + cyclophosphamide $\times$ 6; FEC arm) with a taxane regimen (docetaxel $\times$ 3 followed by epirubicin + docetaxel $\times$ 3; T $\rightarrow$ ET arm).