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Adjuvant therapy in stage IB/II non-small cell lung cancer (NSCLC): final results of a multi-center, double-blind, randomized, placebo-controlled Phase II study evaluating the MAGE-A3 cancer immunotherapeutic

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Background: Even after complete surgical resection, about half of the patients with stage IB or II NSCLC relapse and die within 5 years. Cisplatin-based adjuvant chemotherapy improves overall survival but at the expense of substantial toxicity. A phase II study evaluating the MAGE-A3 cancer immunotherapeutic (i.e. a recombinant MAGE-A3 protein and a novel GSK proprietary adjuvant system) in metastatic melanoma showed a good tolerability and long-lasting clinical objective responses. As about 35% of NSCLCs stages IB or II express MAGE-A3 antigen, post-operative treatment with the MAGE-A3 immunotherapeutic may be a tumour-specific, well tolerated, and effective adjuvant therapy.
Methods: Patients with completely resected, MAGE-A3 (+), stage IB or II NSCLC were randomly assigned to postoperative intramuscular administrations of MAGE-A3 or placebo (2:1), with 5 administrations at 3-week intervals, followed by 8 administrations every 3 months. Randomisation was stratified for stage (IB vs. II), histology (squamous carcinoma vs. other), and lymph-node procedure (sampling vs. dissection). Primary endpoint was disease-free interval (DFI); secondary endpoints were safety, disease-free survival (DFS), and overall survival (OS). This phase II study (249553/004/NCT00290355) was designed to detect a clinically relevant hazard ratio with a 10% one-sided α
Results: 1089 tumour samples were examined, of which 363 expressed the MAGE-A3 gene. 182 patients (122 stage IB, 60 stage II) from 59 centres in 14 European countries were randomised over 2 years. Patient characteristics are as follows: Median age 63 (45−81); 87% male; 65% squamous cell carcinoma; 65% lymph-node dissection. After a median follow-up of 28 months, 67 recurrences were observed. Group comparisons of DFI, DFS, and OS gave respectively a hazard ratio of 0.74 (95% CI 0.44−1.20, p = 0.107), 0.73 (95% CI 0.45−1.16, p = 0.093) and 0.66 (95% CI 0.36−1.20, p = 0.088) in favour of the MAGE-A3 group. Overall, treatment was well tolerated. Subset analysis suggests that lymph node dissection may have a positive effect on survival.
Conclusions: The final analysis of this randomised phase II study shows a positive signal for clinical activity of MAGE-A3 cancer immunotherapeutic as adjuvant treatment in completely resected Stage IB or II NSCLC. The relative improvement in disease-free interval and disease-free survival is 27%. This treatment is well tolerated. Further phase III evaluation in early NSCLC is planned for 2007.

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Transcriptional changes in non-small cell lung cancer are associated with cell adhesion and cell migration processes

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Background: Lung cancer is the main cause of mortality among all malignancies in western countries. The prognosis of the disease is very poor: less than 15% of the patients survive more than 5 years after initial diagnosis of tumors in late stage (III-IV), when mostly metastases are already manifest. The non-small cell lung cancer (NSCLC; 80%) could be widely differentiated in two histologically distinct forms, the adenocarcinoma and the squamous cell carcinoma. Although these tumors are histologically specifiable and may be associated with different patient prognosis, no specific therapy exists. Thus, better diagnostic tools and more efficient and specific therapies are urgently required.
Material and Methods: We have performed a microarray study using Affymetrix U133 Plus 2.0 Arrays comprising 57 lung tumor samples of different histology, as well as lymph node and relapse status. All tissue sections underwent a careful re-analysis of the histopathology, estimation of tumor and stromal content and subsequent macro-dissection of the regions of interest before enrollment into the study. Statistical analysis for microarrays was performed using modified t-Test statistic (SAM) and Gene Ontology statistic. For a subset of 30 genes, gene expression analysis was extended to matched tumor-normal samples using quantitative RT-PCR (Taqman) method. Immunhistochemical analysis of tissue microarrays was performed for a subset of cell junction proteins.
Results: We identified large transcriptomic differences between squamous cell carcinoma and adenocarcinoma affecting distinct cellular processes like cell cycle, DNA replication or cell adhesion. Different subsets of genes coding for cell junctions were found to be deregulated in both histological subtypes. The majority of these genes and associated players of epithelial-mesenchymal transition process could be verified to be upregulated in cancer versus matched normal tissues. In a meta-analysis approach, we applied these signatures to publicly available lung cancer datasets to prioritize candidate genes for cellular assays with regard to cell adhesion, cell migration and metastasis using lung cancer cell-lines.
Conclusion: Histological subtypes of NSCLC can be strongly separated by specific transcription profiles which are relevant for tumor progression processes like cell adhesion, cell migration and metastasis formation.

Oral presentations (Thu, 27 Sep, 11.15−12.30)
Lung cancer (3)

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Venous thromboembolism (VTE) and non-small cell lung cancer (NSCLC): a pooled analysis of National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) trials

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Background: Cancer is a recognized risk factor for venous thromboembolism (VTE), and studies suggest that treatment with anti-neoplastic agents may increase the risk of VTE. We undertook a pooled analysis of NCIC CTG trials to determine whether there is an increased risk of VTE in patients with early and advanced NSCLC, to examine predictive factors for VTE and whether VTE was a prognostic factor.
Methods: Individual patient data from JBR10 (adjuvant vinorelbine/cisplatin [ACT] vs. observation in resected stage IB-II NSCLC), BR18 (paclitaxel/carboplatin [CT] +/− BMS275291 [MMPI] in advanced NSCLC) and BR21 (erlotinib [E] vs. placebo [P] in advanced NSCLC, 2:1 randomization)) were pooled. VTE rates, baseline as well as during-therapy predictors of VTE (including prior history, concomitant medications, obesity, smoking, surgery, gender, anticancer therapy, comorbidity index, transfusions, laboratory values, performance status [PS], hospitalization) and impact of VTE on survival were evaluated for each trial as well as for pooled trials. All comparisons between treatment arms were carried out using a 2-sided 5% alpha test. Kaplan-Meier plots were used to estimate survival distributions, Cox regression analysis for associations of VTE with survival, (adjusted for relevant covariates), while chi-square tests were used for univariate and logistic regression for multivariate analyses.
Results: BR10: (N = 7, 3% VTE, all on ACT); VTE patients were more likely to be obese (morbidly 50% v obese 5% v not 2%, p = 0.001), and to have low platelet counts (low 33% v normal 2% v high 0%, p = 0.007). BR18: 62 patients had VTE (9% on CT+MMPI, 7% on CT p = 0.6); VTE patients were more likely to have had erythropoietin (100% v 8%, p = 0.08), prior VTE (32% v 7%, p = 0.001), anticoagulants (16% v 7.0%, p = 0.008), and less likely to have had vomiting or diarrhea (p = 0.0004), a fall in PS (p < 0.0003), hospitalization (p < 0.0001) or concomitant steroids (p = 0.0004); BR21: 20 patients developed VTE (13 E [3%], 7 P [3%], p = 0.99); the only predictive factor was prior VTE. VTE was not associated with a poorer survival for BR10, while it was for BR18 (HR 1.48, p = 0.006) and BR21 (HR 4.09; p < 0.0001). For BR 21+18 the occurrence of VTE remained prognostic (HR 1.83, p < 0.0001).
Summary: VTE is a frequent event in patients with NSCLC and is associated with obesity, a prior history of VTE and with treatment with chemotherapy, but not EGFR inhibitors, and is prognostic.