54LBA LATE BREAKING ABSTRACT

High coexpression of both the insulin-like growth factor receptor-1 (IGF-1R) and epidermal growth factor receptor (EGFR) correlates with a poor patient prognosis in resected non-small cell lung cancer (NSCLC)

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Background: Following the success of the EGFR inhibitors a renewed interest in IGF-1R inhibitors has emerged. IGF-1R overexpression has been identified in several tumour types and protects cancer cells from apoptosis. Currently, several different approaches are being investigated for targeting the IGF-1R, including small-molecule kinase inhibitors, IGF1R monoclonal antibodies, antisense oligonucleotides and RNA interference. To date, it is not clear what factors influence sensitivity to IGF-1R blockade but it is likely that tumours that respond well to treatment will be those where IGF-1R overexpression results in a poor patient prognosis. Initial data show that tumour type may also determine response to therapy with squamous non-small cell lung cancers responding well to a IGF-1R monoclonal antibody and chemotherapy. The aim of this study is to elucidate the EGFR and IGF-1R expression profile in a cohort of NSCLC patients and correlate the results to patient clinico-pathological data and prognosis.
Methods: EGFR and IGF1R expression were evaluated in 197 NSCLC patients (92 – squamous, 87 – adenocarcinoma, 18 – others) using immunohistochemistry (IHC) analysis. Membraneous staining (% cells × staining intensity) was evaluated by a pathologist and scored as follows: 0 (negative), 1+ (weak), 2+ (moderate) and 3+ (strong). Expression of EGFR and IGF1R were also examined in a panel of cell lines (SKMES1, A549, HCC827, H1819, H1299) and patient samples (10 squamous and 10 adenocarcinomas) using Western Blot analysis.
Results: The panel of 6 NSCLC cell lines examined showed variability in IGF-1R expression. In the fresh frozen resected NSCLC tumours IGF-1R was overexpressed relative to matched normal tissues. Furthermore squamous cell carcinomas had higher levels of expression than adenocarcinomas. Immunohistochemistry analysis demonstrated that squamous cell tumours have higher IGF-1R expression levels than adenocarcinomas (3+/2+ Squamous [70/197] versus 3+/2+ Adenocarcinoma 27/197)] $p < 0.0001$). Patients with squamous cell carcinoma also had higher EGFR expression than those with adenocarcinoma ($p = 0.002$). Patients with EGFR and IGF-1R overexpression had a poorer survival ($p = 0.043$).
Conclusions: Our findings indicate that while EGFR and IGF-1R expression alone are not independent prognostic markers of survival in NSCLC. Taken together overexpression of both proteins correlates to a poor survival. This subset of patients may benefit from treatments cotargeting IGF-1R and EGFR.

55LBA LATE BREAKING ABSTRACT

Randomized phase II trial: Effect of all-trans retinoic acid with chemotherapy based in paclitaxel and cisplatin as first line treatment of patients with advanced non-small cell lung cancer

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Background: Platinum-based chemotherapy (CT) is the standard treatment for advanced non-small-cell lung cancer (NSCLC). Unfortunately, the survival and response rate (RR) to CT is poor. All-trans retinoic acid (ATRA) has tumor-supressive capacity through the activation RAR and RXR receptors. Loss of expression of RAR beta 2 (RAR b2) isoform is associated with human tumor progression in lung cancer. Previous studies have indicated that adding ATRA to CT may improve outcome in advanced NSCLC. The aim of this trial is to evaluate the progression-free survival (PFS), RR and toxicity of low doses of ATRA in addition of paclitaxel and cisplatin and its association with the expression of RAR b2 as a molecular response marker in patients with advanced NSCLC.
Methods: Between April 2005 and October 2007, 107 patients with stage IIIB and IV NSCLC were included to receive Paclitaxel 175 mg/m^2 and Cisplatin 80 mg/m^2 (PC) every 21 days for a maximum of 6 cycles. Patients were randomized to receive ATRA 20 mg/day (RA/PC) or placebo (P/PC) 1 week before treatment until completing two cycles. Imaging studies were performed prior and after two cycles of CT to assess response. RAR b2 expression was analyzed by immunohistochemistry (IHC) and RT-PCR in lung tumoral tissue and in the adjacent lung tissue.
Results: RR for RA/PC was 55.8% (CI 95%, 46.6–64.9%) and for P/PC of 25.4% (CI 95%, 21.3–29.5%, $p = 0.001$). Median of PFS was 8.9 months vs 6.0 months ($p = 0.008$) for RA/PC and P/PC, respectively. The multivariate analysis of PFS adjusted to stage at enrollment showed significant differences in favor to RA/PC group (HR 1.62, CI 95% 1.06−2.5, $p = 0.028$). No significant differences in toxicity grade 3/4 were found between groups except for hypertriglyceridemia (10% vs 0%) in RA/PC ($p = 0.05$). Only 6 tumors were positive for RAR b2 by IHC and RT-PCR in tumor tissue, but remained expressed in adjacent normal tissue.
Conclusions: Adding ATRA to CT could increase RR and PFS in advanced NSCLC patients with an acceptable toxicity profile. A phase III clinical trial is warranted to confirm these findings.

56LBA LATE BREAKING ABSTRACT

Prediction of response to preoperative chemoradiotherapy in rectal cancer by multiplex kinase activity profiling

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Background: Tumor response of rectal cancer to preoperative chemoradiotherapy (CRT) may vary considerably. Recognizing that activity of particular subsets of kinase signaling pathways is a key predictor of radioresponse in experimental tumor models and clinical radiotherapy, this study aimed to determine whether intrinsic kinase activity profiles of tumors might predict individual responses to preoperative CRT in locally advanced rectal cancer (LARC).
Material and Methods: In our phase II trial LARC-RRP; *Locally Advanced Rectal Cancer – Radiation Response Prediction,* ClinicalTrials ID: NCT00278694; radiotherapy was conventionally delivered as 25 daily fractions of 2.0 Gy with concomitant oxaliplatin (50 mg/m^2) once weekly and capecitabine (825 mg/m^2 BID) on radiotherapy days and with surgery performed 6−8 weeks after CRT completion. Pretreatment tumor biopsies were analyzed using microarrays with kinase substrates (Tyrosine Kinase PamChip® arrays; www.pamgene.com) and the resulting substrate phosphorylation patterns were correlated with the individual tumor responses to preoperative CRT as assessed by histomorphologic tumor regression grade (TRG). Class prediction and estimate of prediction performance of TRG scores from phosphopeptide signatures were obtained by partial-least-squares discriminant analysis and leave-one-out cross-validation.
Results: In a study population of 67 individuals, 73% and 15% were scored as good responders (TRG 1−2) or intermediate responders (TRG 3), respectively, whereas 12% were assessed as poor responders (TRG 4−5). In a subset of 7 poor and 12 good responders, treatment outcome was correctly predicted for 95%. Application of the prediction model on the remaining patient samples resulted in correct prediction for 85%. Compared to good and intermediate responders, peptide substrate phosphorylation in poor-responding tumors indicated significantly higher kinase activity mediated by VEGFR, EGFR, and PI3-K/AKT signaling, which is implicated in radioresistance mechanisms of tumor hypoxia and repopulation. Moreover, in the poor-responding tumor biopsies, this kinase activity was significantly inhibited by sunitinib, an inhibitor of VEGFR-mediated signaling.
Conclusion: Multiplex kinase activity profiling may assist in predicting tumor response to preoperative CRT in LARC and may, in addition, provide leads to therapeutic targeting of underlying regulatory mechanisms to countervail radioresistance.

57LBA LATE BREAKING ABSTRACT

Aprepitant (APR) for the prevention of chemotherapy-induced nausea and vomiting (CINV) associated with moderately emetogenic chemotherapy (MEC) in breast and non-breast cancers

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Background: APR was shown previously to be effective in preventing CINV associated with highly emetogenic chemotherapy (HEC) in patients with solid malignancies and with MEC including an anthracycline and cyclophosphamide (AC) in breast cancer patients. This study assessed APR in patients with a variety of tumors receiving a broad range of MEC