

## 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. Membrane 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.

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## 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-suppressive 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<sup>2</sup> and Cisplatin 80 mg/m<sup>2</sup> (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.

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## 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<sup>2</sup>) once weekly and capecitabine (825 mg/m<sup>2</sup> 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 counteract radioresistance.

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## 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

regimens. A planned analysis was performed based on tumor type. This analysis reports the most comprehensive data to date on the efficacy of an APR regimen in patients with cancers other than breast, and receiving predominantly non-AC-based MEC.

**Materials and Methods:** This phase III randomized, gender-stratified, double-blind trial enrolled patients with confirmed malignancies, naive to HEC or MEC agents, who were scheduled to receive at least one MEC agent. Patients received an APR-triple-therapy regimen (APR, ondansetron [OND], and dexamethasone [DEX]) or a control regimen (OND and DEX) administered orally. The primary efficacy endpoint was the proportion of patients with No Vomiting during 120 h post-chemotherapy. Treatment group comparisons were based on a logistic regression model with terms for treatment, region, and gender. Nominal p-values are reported.

**Results:** Among 832 patients in the modified-intent-to-treat population, 53% had breast cancer and 47% other cancer types (primarily colorectal, lung, or ovarian). Overall, more patients experienced No Vomiting in the APR group, regardless of whether they had breast cancer or another cancer type (differences of 16.6% and 10.8% vs. control, respectively, see table). Similar trends were seen in subsets of breast cancer patients receiving AC or non-AC chemotherapy, and in non-breast cancer patients receiving non-AC-based regimens. Overall, the incidences of adverse events were generally similar in the APR (61.9%) and control groups (66.5%).

**Conclusions:** The benefit of APR triple therapy has been shown to extend to non-breast cancer patients receiving non-AC based MEC, including those receiving oxaliplatin- and carboplatin-based therapy. In these patients, the APR regimen provided better efficacy over the control regimen in the prevention of CINV.

| No vomiting in overall phase<br>(0–120 h post-chemotherapy) | APR<br>regimen<br>% (n/m) | Control<br>regimen<br>% (n/m) | p-value |
|---|---------------------------|-------------------------------|---------|
| Breast cancer (all regimens)                                | 69.3<br>(151/218)         | 52.7<br>(116/220)             | 0.0004  |
| Breast cancer (AC)  | 67.7<br>(131/193)         | 51.3<br>(97/189)              | 0.0014  |
| Breast cancer (non-AC)                                      | 80.0<br>(20/25)           | 65.2<br>(15/23)               | 0.21    |
| Other cancers (all regimens)                                | 83.4<br>(176/211)         | 72.6<br>(138/190)             | 0.006   |
| Other cancers (carboplatin)                                 | 84.3<br>(86/102)          | 70.0<br>(63/90)               | 0.016   |
| Other cancers (oxaliplatin)                                 | 81.9<br>(68/83)           | 74.6<br>(53/71)               | 0.32    |
| Other cancers (any other chemo)                             | 87.0<br>(20/23)           | 80.0<br>(20/25)               | 0.28    |

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## LATE BREAKING ABSTRACT

### Prospective observational study of the proportion hospitalised cancer patients at risk of refeeding syndrome

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**Background:** Refeeding syndrome (RFS) has been recognised as a serious biochemical condition resulting from the sudden re-feeding of malnourished patients (Crook and Swaminathan 1996). Little exists in the oncologic literature about RFS (Marinella 2008). The aim of this study was to identify the proportion of cancer inpatients who were at risk from RFS.

**Materials and Methods:** In this study, RFS was defined as "A collection of electrolyte disturbances, including one or more of the following: hypophosphataemia (<0.7 mmol/l), hypokalaemia (<3.5 mmol/l), hypomagnesa (<0.5 mmol/l) occurring 2–4 days post dietetic intervention i.e. oral nutrition support, enteral or parenteral nutrition". A prospective observational study was undertaken over a 3 month period (March – May 2009). A total of approximately 1400 cancer patients hospital admission were screened for risk of malnutrition using a Trust screening tool based on validated McDougall et al 2008. High risk patients were reviewed by dietitians and blood results were obtained from patients' electronic records.

**Results:** Eleven percent (154/1400) of patients had a nutritional risk score >10 (high risk); 62% (95/154) were included in the study, 10% (16/154) of patients were excluded due to terminal stages of illness or death (unrelated to RFS) and data for 28% (43/154) patients was unobtainable. Thirty two percent (31/95) of patients were found to be at a high risk of developing RFS (NICE 2006) of which 45% (14/31) developed RFS. Amongst patients who developed RFS; 2 had refractory myeloma, 2 lymphoma, 3 head and neck cancer, 3 rectal cancer, 3 lung cancer and 1 prostate cancer. Mean weight was 57kg (SD 12.3), mean BMI 20 (SD 3.3) and mean weight loss over 3–6 months was 11.6% (SD 7.7).

**Conclusions:** This study found that RFS could occur in 45% of high-risk malnourished cancer patients. Recognition and appropriate management is mandatory in the treatment of this potentially fatal condition.