In order to assess the progression free-survival (PFS) time, miRNA expression levels were categorized in quartiles. In analogy to their relationship with clinical benefit, the same three miRNAs were also associated with longer PFS: hsa-miR-30a-3p (hazard ratio [HR]: 0.51, 95% CI: 0.34−0.76; P = 0.001), hsa-miR-30c (HR: 0.47, 95% CI: 0.31−0.70; P < 0.001), and hsa-miR-182 (HR: 0.57, 95% CI: 0.37−0.86; P = 0.008). Global testing using available global gene expression data significantly associated the 3 predictive miRNAs with differential gene expression of HER-2, Rac-1 and Ceramide signaling pathways.
Conclusion: This study shows associations between hsa-miR-30c, hsa-miR-30a-3p and hsa-miR-182 expression levels and clinical benefit to treatment with first-line tamoxifen for recurrent BC and describes pathways putatively involved in these associations. Assessment of these miRNA levels and their pathways in primary tumors could help to improve treatment strategies for patients with recurrent ER+ breast cancers.

PP122

Intraoperative tissue fluorescence using 5-aminolevolinic acid (ALA) is more sensitive than contrast-MRI or amino acid (FET)-PET guided glioblastoma (GBM) surgery

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Background: The ability of 5-ALA to visualize white matter infiltration zones of GBM compared to MRI contrast or [18F]fluoroethyltyrosine positron emission tomography (PET) was investigated.
Materials and Methods: Fluorescence tissue margins were mapped intraoperatively by neuronavigation and compared to pre- and postoperative MRI and FET-PET scans in 3 glioblastoma patients (2 temporal, 1 fronto-central tumor).
Results: In all patients, the intraoperatively detected 5 ALA fluorescence exceeded the MRI contrast tumor areas and FET-PET uptake, verified by intraoperative neuronavigation. Furthermore, all patients received complete resection of contrast affine tumor parts, which was verified by contrast MRI scans within 24 hours postoperatively. Although intraoperative fluorescence tissue was generously left in place, because it was estimated as tissue at risk for neurological deterioration, no contrast affine tissue could be detected by postoperative MRI. Additionally, postoperative FET-PET uptake was demonstrated only in one patient as a small residual spot. FET-PET did not show any uptake at the intraoperatively mapped large marginal areas of 5 ALA fluorescence, left in place in account of neurological preservation
Conclusion: Our findings demonstrate that 5 ALA fluorescence is more sensitive than FET-PET and MRI contrast uptake in detecting glioblastoma multiforme white matter infiltration zones.

PP127

INHANCE (Iressa™ Novel Head and Neck Chemotherapy Evaluation) randomised phase II trial: clinical findings and associated translational research into EGFR-related biomarkers in tumour and skin biopsies

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Background: The INHANCE randomised phase II trial (1839IL0544) explored the feasibility and benefits of adding an EGFR tyrosine kinase inhibitor (gefitinib, AstraZeneca, Macclesfield, UK) to induction chemotherapy with cisplatin and 5-fluorouracil in patients with newly diagnosed squamous cell carcinoma of the head and neck. Associated translational research enabled the unique investigation of EGFR-related signalling changes induced by chemotherapy and a comparison with those elicited by chemotherapy plus gefitinib in randomised therapy-naïve patients.
Materials and Methods: Patients were openly randomised to two cycles (q21 days) of cisplatin (100 mg/m^2 day 1) and 5-fluorouracil (1g/m^2 days 1−4) with or without oral daily gefitinib (250 mg days 1−42). Tumour and skin biopsies were collected pre-treatment and after 14 days of therapy. Given the limitations of immunohistochemistry, we analysed EGFR-related signalling by western blotting and a novel electrochemiluminescent immunoassay (Meso Scale Discovery, Gaithersburg, MA, USA) that we have previously validated in vitro and in vivo.
Results: Thirty-eight patients were randomised. The combination was well tolerated. 53% and 71% of patients donated paired tumour and skin biopsies respectively. Each biopsy yielded sufficient lysate for two western blots and three immunoassays. Using the two independent techniques, there was good concordance between expression and activation of EGFR and AKT in 80% and 86% of tumour biopsies respectively. Signalling changes in skin biopsies only reflected those seen in tumour biopsies in 50% of patients. Two of three patients treated with chemotherapy plus gefitinib who developed a rash demonstrated a reduction in EGFR phosphorylation in tumour, but not skin, biopsies.
Conclusion: Correlation with western blotting shows that the electrochemiluminescent immunoassay is a useful method for quantifying signalling changes in small volume clinical samples but skin was not a reliable surrogate tissue for tumour. Cytotoxic chemotherapy alone elicited changes in EGFR phosphorylation that confounded the interpretation of gefitinib-induced alterations. We conclude that biomarkers optimised for the evaluation of targeted therapies as single agents may be compromised when combined with conventional therapy.

PP63

Predictive markers in patients with upper gastrointestinal (GI) cancers treated with erlotinib and bevacizumab in a multicenter phase II trial

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Background: We investigated the role of several growth factors, growth factor receptors, and markers of ischemia as predictors of response and survival in patients treated with VEGF and EGFR targeted therapy.
Materials and Methods: This exploratory study evaluated the predictive value of plasma levels of vascular endothelial growth factor A (VEGF-A), platelet derived growth factor AB and BB (PDGF-AB and PDGF-BB), soluble Fms-related tyrosine kinase 1 (sFlt-1 or sVEGFR-1), growth differentiation factor 15 (GDF15), hepatocyte growth factor (HGF), high sensitivity troponin T (hsTnT), and pro brain natriuretic peptide (proBNP) in patients with advanced upper GI cancer in progression after chemotherapy. Patients were treated with drugs targeting angiogenesis (bevacizumab) and the EGFR pathway (erlotinib) in a multicenter phase II trial (ASCO GI 2009, abstract #170). Plasma was collected at baseline and weekly during the first 4 weeks. Plasma was analysed using quantitative immunoassays. Results of baseline samples and changes in plasma levels of the markers were correlated to progression-free survival (PFS) and clinical benefit (CB), defined as stable disease (SD) or partial response (PR).
Results: Baseline plasma was available in 79 out of 100 patients (median age 62 [25−78]) with carcinoma in esophagus (36%) (adeno [30%], squamous [6%]), stomach (12%), pancreas (33%), and biliary tract (19%). Three patients had PR, 28 SD, 22 PD, and 26 were not evaluable. Patients with baseline PDGF-AB in the upper quartile had significantly longer PFS (HR: 0.45, 95% CI: 0.23–0.85). Patients with proBNP below median had significantly better PFS than patients with levels above (HR: 1.73, 95% CI: 1.06–2.83). The remaining markers failed to predict CB or PFS.
We observed a decrease of VEGF-A (11.36, 95% CI: 6.16–32.41), HGF (0.07, 95% CI: 0.01–0.28), and GDF15 (0.33, 95% CI: 0.08–1.31), and a trend towards decrease of proBNP (22.34, 95% CI: −0.68–159.29) between baseline and after 1 week of therapy. However, VEGF-A was in most cases undetectable in plasma after start of therapy.
Conclusion: Decrease in plasma levels of VEGF-A, HGF, proBNP, and GDF15 was observed during EGFR/VEGF-targeted therapy. The high frequency of undetectable VEGF-A after initiation of therapy could be attributed to its binding to bevacizumab.
High levels of PDGF-AB and low levels of proBNP seem to predict longer PFS. These findings are of biological and therapeutic relevance and warrants further investigations.

PP103

RT-PCR-based UCA1 expression detection in urine samples as non-invasive reliable method for urothelial cancer diagnosis

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Background: Bladder cancer is among the five most common malignancies in industrialized countries. There are currently no satisfactory markers