EGFR and PIK3CA alterations do not seem predict the efficacy of chemoradiation in SCAC patients, suggesting that other molecular markers should be investigated.
The presence of both EGFR gene deregulation and high frequency of PI3KCA mutation suggests that patients with SCAC could more benefit from tailored therapies against these two targets.

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Plasma biomarkers for early prediction of chemotherapy response and toxicity in colorectal cancer

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Background: Accurate predictors of chemotherapy response and toxicity are required to improve the safety, efficacy and costs of cancer treatment in colorectal cancer (CRC). Our aims were to investigate the utility of plasma proteomic profiling using multiple reaction monitoring mass spectrometry (MRM-MS) for predicting early haematological toxicity and response for patients receiving chemotherapy.
Materials and Methods: Patients with locally advanced and metastatic CRC receiving chemotherapy were enrolled. Plasma collection was performed at day 1, day 3 and day 15 of treatment. Toxicity assessments (NCI Criteria version 3.0) were prospectively collected for all patients and treatment response (RECIST Criteria) for patients with metastatic disease. MRM-MS assays were designed for 39 peptides representing 31 liver derived plasma proteins with roles in inflammation and/or cancer. Two-sample t-test was used to assess statistically significant fold change differences ($p < 0.05$) between sample days for: (1) absence or presence of $\geqslant$Grade 2 neutropenia after two cycles and (2) responders (CR and PR) versus non-responders (SD or PD).
Results: Fifty one patients have been enrolled in the trial. Sixty one percent of patients were male with 45% having metastatic disease. Plasma proteomic profiling for 39 peptides was performed for 16 patients at Day 1, Day 3 and Day 15 selected due to their toxicity and response to treatment. The greatest change in protein levels was observed between Day 3 and 15 with approximately 9% of proteins showing a 1.5 fold or greater change. Some proteins such as serum amyloid A showed more than 200-fold change in level. Preliminary results indicate there are statistically significant differences in protein expression for patients with (1) neutropenia versus those without neutropenia and (2) clinical responders versus non-responders in those with metastatic disease.
Discussion: Our results are encouraging for the use of plasma biomarkers using this technique for early prediction of moderate to severe neutropenia and chemotherapeutic response in CRC. These data require validation in large prospective cohorts of colorectal cancer patients.

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Associations between genetic KDR polymorphisms and survival in patients with metastatic cancer treated with antiangiogenic therapy

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Background: Vascular endothelial growth factor (VEGF) and its receptors KDR (VEGFr-2) have important roles in angiogenesis, predicting risk and prognosis in several solids tumor. VEGFr-2 located on chromosome 4 (4q11-q12) is organized into 30 exons separated by 29 introns. Recently the VEGF-2578 AA and VEGF-1154 AA genotypes were associated with a superior median overall survival when using bevacizumab in metastatic breast cancer. We investigated the association of VEGFr-2 polymorphisms to efficacy and toxicity in patients with antiangiogenic therapy.
Methods: We performed genotype for selected VEGFr-2 polymorphisms in promoter regions 5'UTR, 3'UTR; in exons 7, 8, 9, 11, 16, 17, 18, 21, 27, 30 and introns 9, 17, 20. DNA was extracted from venous blood of 44 patients with non-curable solid tumors who have received treatment with bevacizumab (B) N = 20 (45%) or raf kinase inhibitors 55%; vatalanib (PTK-787) N = 3, sunitinib (SU011248) N = 6, sorafenib (BAY 43–9006) N = 13, ZD6474 N = 1 and AMG706 N = 1. Kaplan-Meier survival analysis was used to assess the association between VEGFr-2 staining and either progression-free survival (PFS) or overall survival (OS).
Results: 44 patients have received a median of 6 (1−19) cycles of treatment, 72% was used simultaneously with QT. According to the criteria of NCI-CTC the severe toxicity G3−4 occurred in 47%, 9% with a definite suspension of the drug. The toxicity was not associated with VEGFr-2 genotypes. Efficacy; 5/44 patients (11%) had complete response and 11/44 (22%) partial responses by RECIST criteria. With a median follow up of 12 months, the ILP was 8.5 months dt (5.8). The analysis of VEGFr-2 polymorphisms identifies the variant AA of the intron-20 rs2219471 with a significant difference in PFS and OS regarding their ancestral variant AG.
Conclusions: Our data suggest that VEGF-R polymorphism can be a predictor of clinical outcomes in antiangiogénic therapy. However, these findings require further prospective investigation.

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Detection of cytokeratin-19 mRNA-positive cells in peripheral blood and bone marrow of patients with operable breast cancer

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Purpose: To compare the detection rates and evaluate the clinical relevance of cytokeratin-19 (CK-19) mRNA-positive cells in bone marrow (disseminated tumor cells;DTCs) and peripheral blood (circulating tumor cells;CTCs) of patients with early breast cancer.
Patients and Methods: Paired samples of peripheral blood and bone marrow were concomitantly obtained from 165 patients with stage I/II breast cancer before the initiation of adjuvant chemotherapy. In 84 patients, paired blood and bone marrow samples were available post-chemotherapy. The detection of CK-19 mRNA-positive CTCs and DTCs was assessed by real-time PCR.
Results: CK-19 mRNA-positive CTCs and DTCs could be detected in 55.2% and 57.6% of patients pre- chemotherapy, respectively. Post-chemotherapy, CTCs and DTCs were identified in 44 (52.4%) and 43 (51.2%) of the 84 patients, respectively. There was a 93.9% ($p = 0.344$) and 72.6% ($p = 0.999$) concordance between blood and bone marrow samples pre- and post-chemotherapy, respectively, when classifying the results as either positive or negative. The detection of CK-19 mRNA-positive CTCs and DTCs before chemotherapy was associated with decreased overall survival ($p = 0.024$ and $p = 0.015$, respectively), whereas, their simultaneous detection was associated with an increased incidence of disease-related death and decreased overall survival ($p = 0.016$). The detection of either CTCs and/or DTCs was an independent factor ($p = 0.040$) associated with decreased survival.
Conclusions: The above results indicate a strong correlation between the presence of CTCs and DTCs evaluated by RT-PCR for CK-19 mRNA in patients with early breast cancer. The detection of CTCs using this assay is able to deliver clinically relevant information that is not inferior to the detection of DTCs in the bone marrow.

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Low or undetectable levels of MPL (thrombopoietin receptor gene) mRNA expression on tumour cell lines and primary tumours compared with EPOR, ERBB2, and IGF1R

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Background: A better understanding of the effects of recently discovered thrombopoietin receptor (TpoR) agonists on tumors is needed. By binding to different parts of TpoR, TpoR agonists signal differently. Eltrombopag, a non-peptide TpoR agonist, has been shown to decrease proliferation of leukemia and lymphoma cells in vitro. Although TpoR expression on megakaryocytic cells is well documented, little quantitative data exist for expression on tumors.
Materials and Methods: Quantitative RT-PCR (qRT-PCR) was performed on 378 tumor cell lines available from ATCC and the German Collection of Microorganisms and Cell Cultures (DSMZ). Microarray data were examined from 118 breast cancer, 29 non-small cell lung cancer (NSCLC), and 151 renal cell carcinoma (RCC) samples. Robust multiarray average (RMA) analysis was used to determine relative mRNA expression levels. In addition, qRT-PCR analysis was performed for *MPL* (TpoR gene) expression on ~160 tumor samples each, from subjects with prostate, ovarian, lung, and breast cancers. Protein levels were determined by western blot analyses on several tumor cell lines.
Results: *MPL* was consistently expressed at low or undetectable levels in the tumor cell lines with the exception of 3 cell lines with >9500 normalized abundance: HEL 92.1.7, KG-1 (2 erythroleukemia cell lines), and NCI-H510 (lung cancer cell line). Western blot analyses showed that the high levels