oncogene. The tumors were characterized for molecular characteristics, histologic phenotypes and angiogenesis, and expended in vivo for multiple in vivo pharmacological studies. Like human tumor populations, this population based tumor model exhibited significant inter-tumor variation in gene expression and tumor microvasculature. We therefore deployed the model for drug response biomarker discovery.
Results: Treatment of a subset of the tumors with the potent selective VEGFR inhibitor tivozanib which is currently in phase 3 clinical trial for kidney cancer revealed significant variation in response. Pharmacogenomic analysis using a novel coherence based bioinformatics approach revealed the association of a specific biological phenotype comprising tumor myeloid infiltration with drug resistance. A multi-gene signature derived from the biological phenotype has been used to query genetic data of human tumor populations. The result suggests that the drug resistance phenotype is represented in a subset of all solid tumor types examined but frequencies vary. We have subsequently developed a single, semi-quantitative immunohistochemistry (IHC) marker that represents the drug resistance phenotype. In a retrospective analysis of RCC patients that have received tivozanib monotherapy a significant correlation between the IHC biomarker and drug response (by RECIST) has been observed.
Conclusion: These results provide a promising candidate predictive biomarker for tivozanib activity in patients and indicate the utility of tumor population based models for biomarker discovery.

PP 55

Serum levels of the extracellular domain of HER-2 receptor in osteosarcoma patients

I. Lugowska, W. Woźniak, K. Szamotulska, J. Ambroszkiewicz, J. Gajewska, P. Rutkowski. *Maria Sklodowska Curie Memorial Cancer Centre − Institute of Oncology, Warsaw, Poland*

Background: The prognostic role of HER-2 expression in osteosarcoma is controversial. The aim of the study was to asses a clinical value of the serum extracellular domain of HER-2 receptor (ECD/HER-2) level and its correlation with disease progression in patients with osteosarcoma.
Materials and Methods: 33 patients (aged 6−18 years, median 15 years) with primary osteosarcoma were analyzed; 13 were metastatic at presentation. Follow up period was 12−44 months; median 22 months. ECD/HER-2 levels were analyzed by ELISA method four times: at the time of diagnosis (1), before surgery of primary site (2), after surgery (3) and at the end of treatment 6−9 month since diagnosis (4). In 12 patients, tumor biopsy samples were available for assessment of the immunohistochemical HER-2 expression. The disease progression was confirmed by the CT scan and bone scan. The poor result of ECD/HER-2 value was calculated as higher than 5.5 ng/mL and/or elevated more than +1 ng/mL.
Results: Disease progression was observed in 10 patients, 7 of them died. 8/10 patient who progressed during treatment, had elevated ECD/HER-2 in serum. In 19/23 patient with SD/PR decreasing levels of ECD/HER-2 was observed; $P = 0.001$. 6/7 patients who died had the ECD/HER-2 elevated during treatment or at the end of treatment. There was no relationship between ECD/HER-2 serum level and HER-2 expression in biopsy samples. Immunohistochemical expression of HER-2 did not correlate with treatment results.
Conclusion: This pilot study shows the possible clinical value of ECD/HER-2 assessment in serum of patients with osteosarcoma.

PP 68

Cytokines' profiles to predict chemotherapy outcome in castration resistant prostate cancer (CRPC)

K. Mahon, S. Breit, D. Brown, M. Molloy, G. Marx, M. Boyer, M. Stockler, S. Henshall, R. Sutherland, L. Horvath. *Sydney Cancer Centre, Royal Prince Alfred Hospital, Newtown, Australia*

Background: Chemotherapy improves symptoms and survival in advanced CRPC, however, around 50% of patients have chemoresistant disease. Early markers of chemoresistance will allow cessation of ineffective therapy and avoid toxicity. While MIC-1 and IL-6 may be markers of response, comprehensive cytokine evaluation has not been performed. This study examined whether early changes in cytokine levels can predict chemoresistance and clinical outcome.
Materials and Methods: Plasma/serum samples pre and post cycle 1 chemotherapy were collected from 59 men with metastatic CRPC (55 docetaxel, 7 mitoxantrone). Levels of 27 cytokines were measured using a bead-based immunoassay. MIC-1 levels were measured by ELISA. Patients were grouped as clinical responders (PR + SD) and non-responders (PD) based on PSA response criteria (PD >25% PSA increase over treatment course if no PSA response). The associations between cytokine levels, response groups and overall survival (OS) were assessed by non-parametric tests and Cox regression survival analysis.
Results: After one cycle of chemotherapy, non-responders had significantly greater increases in 10 cytokines from baseline compared with those who responded to treatment (MIC-1 $p = 0.003$; IL1ra $p = 0.004$; IL1b $p = 0.01$; IL4 $p < 0.001$; IL5 $p = 0.041$; IL6 $p = 0.003$; IL7 $p = 0.009$; IL8 $p = 0.017$; IL12 $p = 0.004$; IFN gamma $p = 0.001$). At a median survival of 15 months with 49 deaths, increases in IL8 (HR 2.4, 95% CI 1.1−5.0; $p = 0.02$) and IFN gamma (HR 2.6, 95% CI 1.3−5.2; $p = 0.009$) levels by more than 40% from baseline after one chemotherapy cycle were associated with poorer OS. Higher baseline MIC-1 levels also predicted shorter OS (HR 1.6, 95% CI 1.3−2.0; $p < 0.0001$). In a multivariate model including presence of visceral metastases ($p = 0.02$), Gleason score ($p = 0.1$), baseline ALP ($p = 0.2$), baseline Hb ($p = 0.02$) and baseline PSA ($p = 0.76$), baseline MIC-1 levels were an independent predictor of survival (HR 2.0, 95% CI 1.3−3.1; $p = 0.002$).
Conclusion: Early changes in circulating levels of cytokines were associated with chemoresistance in men with CRPC. Additional associations between OS, baseline MIC-1 levels and changes in IL8 and IFN gamma levels suggest inflammation influences outcomes in men with CRPC treated with chemotherapy.

PP 96

NHERF1 in advanced colorectal cancer: its interaction with HIF-1α and TWIST1 plays an important role in synchronous lymph node and liver metastases

A. Malfettone, C. Saponaro, R. Daprile, G. Simone, A. Paradiso, A. Mangia. *National Cancer Centre − Istituto Tumori "G. Paolo II" Bari, Bari, Italy*

Background: Colorectal cancer (CRC) is one of the major malignancies worldwide and recurrence and metastasis is the leading cause of death in CRC patients. Despite recent advances, characterization of new potential biomarker may be useful for the outcome prediction and fundamental to correct management of the disease. NHERF1, a potential candidate of clinical relevance for breast cancer, has been shown to be a new player in CRC progression, promoting Wnt signaling pathway by direct interaction with β-catenin. TWIST, a basic helix-loop-helix transcription factor, is essential in mediating cancer metastasis through the epithelial–mesenchymal transition (EMT) and, recently, a new finding showed that TWIST is critical for hypoxia-mediated EMT. Aim of this study was to investigate the correlation among the expression of NHERF1, HIF-1α, and TWIST1 in metastatic CRC.
Materials and Methods: We assayed NHERF1, HIF-1α, and TWIST1 protein expressions by immunohistochemistry in 51 patients diagnosed with Stage IV CRC, whose distant non-tumoral tissues (DNT), primary tumor (T) and adjacent non-tumoral tissue (NT), lymph node (LnM) and liver metastases (LM) were available.
Results: A shift of NHERF1 from the apical membrane of DNT and NT, to cytoplasmic and nuclear compartments of T, LnM and LM was noticed. Cytoplasmic NHERF1 expression was statistically higher in T, LnM and LM than DNT and NT ($P < 0.0001$). Nuclear NHERF1, such as HIF-1α, was found significantly overexpressed in T and metastatic compartments compared to DNT ($P < 0.0001$). TWIST1 is upregulated in tumor compared with normal tissue and protein expression was significantly higher in T than LnM and LM ($P < 0.0001$). Spearman's rank test showed that nuclear NHERF1 was directly correlated to TWIST1 in T ($P = 0.015$, $r = 0.339$), and, a significant association between HIF-1α and TWIST1 was also noticed in T ($P = 0.016$, $r = 0.365$).
Conclusion: These results indicate that NHERF1 expression results strongly related to the hypoxic microenvironment of metastatic CRC. Tumor progression and metastasis are mediated by a key signaling pathway involving nuclear NHERF1 together with HIF-1α and TWIST1. Thus, we propose nuclear NHERF1 as a new diagnostic marker of advanced malignancy.

PP 11

Correlation between both serum osteopontin/osteonectin and bone remodelling parameters, inflammatory/metabolic variables and survival in metastatic cancer patients with tumors at different sites

G. Mantovani, C. Madeddu, G. Astara, L. Demurtas, G. Antoni, R. Serpe, V. Ruggiero. *Department of Medical Oncology, University of Cagliari, Italy, Cagliari, Italy*

Background: Osteopontin (OPN) is a secreted, integrin-binding phosphoprotein that has been correlated with tumor grade and stage and disease progression in several tumor types. High OPN levels have been clinically correlated with metastatic bone disease and bone resorption in cancer patients. The secreted protein, acidic and rich in cystein (SPARC) is closely related to progression, invasion, angiogenesis and metastatic process of several malignant tumors. The aim of the study was to verify in a population of advanced cancer patients with tumors at different sites whether there is a correlation between circulating levels of OPN and SPARC