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The role of vascular endothelial growth factor (VEGF) and VEGF-receptors genotyping in guiding the metastatic process in radically resected gastric cancer patients

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Background: In radically resected gastric cancer the possibility to predict the site of relapse could be clinically relevant for the selection of post-surgical management. We previously demonstrated that tumour integrins genotyping is involved in determining the metastatic sites. Preclinical studies suggested that tumour angiogenesis may also be crucial for the metastatic process of gastric cancer cells. We then investigated the role of VEGFs and VEGF receptors genotyping in determining either peritoneal carcinosis or hematogenous metastases in radically resected gastric cancer patients.
Materials and Methods: Genotyping for VEGF-A, VEGF-C and VEGFR-1,2,3 was carried out on pT4a radically resected gastric tumours recurring with either peritoneal-only carcinosis or hematogenous metastases. Tumour genotyping for integrins was also performed according to our previous findings.
Results: 101 patients fulfilled the inclusion criteria: 57 with peritoneal carcinomatosis only and 44 with hematogenous spread only. At multivariate analysis, intestinal histology and the AC genotype of rs699947 (VEGFA) showed to independently correlate with hematogenous metastases, whereas diffuse histology and the AA genotype of rs2269772 (ITGA) independently correlated with peritoneal-only diffusion ($p = 0.001$).
Conclusion: Our results seem to indicate that combining information from genotyping of rs699947 (VEGFA, AC), rs2269772 (ITGA, AA) and tumour histology could allow clinicians to individuate gastric cancer at high risk for recurrence either with peritoneal or hematogenous metastases. The selection tool deriving from this analysis may allow an optimal use of the available treatment strategies in these patients.

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Register trial of sorafenib (S) for patients (pts) with metastatic uveal melanoma (metUvMel)

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Background: There is no effective systemic therapy for patients (pts) with metastatic uveal melanoma (metUvMel). Due to the paucity of clinical trials pts are frequently offered individual treatment options. We have analyzed the outcome of pts treated for metUvMel with the oral multikinase inhibitor sorafenib (S) in an IEC-approved register trial of the West German Cancer Center, a national reference center for uveal melanomas.
Materials and Methods: Pts with metUvMel were treated with S [at a dose of 400 mg bid in the first group (G1) and of 200 mg bid in the second group (G2)]. Overall survival (OS) and time to symptomatic progression (TTPsymp) were studied as primary outcome parameters. Secondary outcomes included time to radiologic progression (TTPrad) according to CT and safety. In addition, digital contrast-enhanced NMR (DCE-NMR) and contrast-enhanced ultrasound (CEUS) of liver metastases were performed in selected pts.
Results: A total of 62 pts (median age 63 yrs, range 35−83 yrs; 31 female [50%], 31 male [50%], ECOG 0 44 pts [71%], ECOG 1 15 pts [26%], ECOG 2 2 pts [3%]) were included in the analysis on an intent to treat basis (ITT). Fortysix pts had no prior systemic treatment (74%). Metastatic sites included liver in 60 pts (97%) in addition to other organs in 20 pts (32%). Only two pts (3%) had exclusively extrahepatic metastases. Following 4 CTC-Grade 4 toxicities [hand-foot-syndrome (HFS) and/or diarrhea] in the first 31 pts (G1) (13%), the starting dose of S was reduced to 200 mg twice daily in the subsequent 31 pts (G2) effectively preventing further severe side effects. Median OS was 10.8 mths (CI 6.1–15.1 mths) in G1 and 14.0 mths (CI 6.4-nd mths) in G2, median TTPrad was 5.0 mths (CI 3.1−8.9 mths) in G1 and 4,5 mths (CI 1.5−6.0 mths) in G2 and TTPsymp was 4.1 mths (CI 3.1−5.2 mths) in G1 and 7.1 mths (CI 3.2–10.6 mths) in G2 (Wilcoxon 0.043), respectively.
Conclusion: S at a dose of 200 mg bid is safe in pts with metUvMel predominantly metastatic to the liver and seems to be effective with a median OS of more than 10 mths. Treatment results are encouraging in an orphan malignant disease without established palliative systemic treatment options. A multicenter randomized discontinuation trial with S in pts with metUvMel will be performed.

PP 72

Angiogenesis-related cytokines as potential predictive biomarkers in a phase II trial evaluating everolimus efficacy in locally advanced or metastatic Transitional Carcinoma Cell

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Background: Dysregulation of mammalian Target of Rapamycin (mTOR) pathway and subsequent angiogenesis activation play a role in Transitional Carcinoma Cell (TCC). Despite growing interest for mTOR inhibitors in cancer, there is up to now no potential biomarker able to predict disease control. Here, we evaluated in a phase II trial the efficacy of the mTOR inhibitor everolimus in patients with palliative TCC after failure of platinum-based therapy and we explored potential angiogenesis-related plasma proteins as predictive biomarkers.
Materials and Methods: Patients with locally advanced or metastatic TCC received everolimus 10 mg/day continuously until progressive disease (PD) or unacceptable toxicity. Primary endpoints were control disease rate, including complete response (CR), partial response (PR) or stable disease (SD) at 8 weeks. Plasma samples were collected on day 1 (baseline before treatment), day 28 (during treatment), and at PD. A screening of 55 angiogenesis-related proteins was performed in plasma by cytokine arrays and most significant results were confirmed with dedicated ELISA.
Results: 37 patients (pts) were included. Confirmed PR was observed in 2 pts and SD in 8 pts, resulting in a disease control rate of 27% at 8 wks. Analyzing changes in plasma cytokine concentrations between baseline and day 28, we found that everolimus induces globally an increase in the angiogenesis inhibitor angiostatin (+ 114%; $p < 0.0001$). In pts with controlled disease, we observed an early decrease in two markers of tumor vessel maturation, namely angiopoietin-1 (−84%; $p = 0.01$) and PDGF-AB (−64%; $p = 0.0036$) compared to pts with non-controlled disease. The tumor endothelial cell marker endoglin showed an increase in pts with non-controlled disease (+19%; $p = 0.06$) compared to pts with controlled disease (−17%; $p = 0.27$). Moreover, baseline levels of angiopoietin-1 were much higher in pts with controlled disease than in pts with non-controlled disease (+267%; $p = 0.011$). Interestingly, in the 2 pts with PR, an increase in angiopoietin-1 (+800%), PDGF-AA (+300%) and PDGF-AB (+400%) levels were observed at the time of PD (vs measurements at day 28).
Conclusion: Everolimus exerts antitumor activity in advanced TCC, through a likely anti-angiogenic activity. Angiopoietin-1 appears as a potential biomarker to predict and track such response and should be considered in further clinical trials.

PP 60

Targeting hyaluronan in tumor stroma. Interim translational and biomarker evaluations of pegylated hyaluronidase (PEGPH20) in animal models and patients with advanced solid tumors

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Background: Hyaluronan (HA), a component of the tumor matrix, is present in many solid tumors (T). T's characterized by the accumulation of HA have high interstitial fluid pressure (IFP) that inhibits penetration of chemotherapeutics. PEGPH20 (P) has been shown to remove HA-rich T extracellular matrices in vitro and in vivo xenograft T models. P-mediated depletion of HA in HA+ xenografts reduced T IFP/water content, inhibited T growth, and increased efficacy of chemotherapy. Phase 1 (Ph1) trials currently utilize biomarkers to evaluate P in vivo activity.
Materials and Methods: Two Ph1 studies in patients (PTS) with advanced solid T's refractory to prior therapy assessed the safety, tolerability, pharmacokinetics and pharmacodynamics of single-agent IV P. Dosing in Study 1 was $1\times$/21 d and in Study 2 is $2\times$/wk $\times$ 4 wks and $1\times$/wk thereafter in combination with dexamethasone. Biomarkers evaluated include histochemistry to identify HA status of T's, Apparent Diffusion Coefficient (ADC)/Dynamic Contrast Enhancement (DCE)-MRI of T/normal tissue to assess impact on T water diffusion, and serum HA to demonstrate enzymatic activity of P.
Results: Activity of P was reflected by detection of HA catabolites in plasma. Systemic exposure of HA catabolites increased after single treatment and was dependent on the dose of P. HA concentrations were elevated 100-fold in patients treated with 50 μg/kg P. Repeat dosing with P resulted in sustained plasma concentrations of HA catabolites. ADC-MRI results suggested increased diffusion within T, and DCE-MRI (Ktrans) analysis suggested elevated T perfusion within 24 hours of P dosing. Histochemistry with a HA binding protein demonstrated the ability of P to reduce pericellular and stromal HA after 4 wks of treatment. Plasma and T HA results were consistent between murine xenograft models and humans.