Results: The frequency of the GG, GA and AA genotypes were 58.2%, 31.2% and 10.6%, respectively. We found that GG/GA genotypes were present in 96.6% of cases with advanced disease (stages III-IV) and in 85.6% of cases with early disease (stages I-II) and these differences were statistically significant (OR = 4.8, $P = 0.026$). After adjustment for gender and age ($\leqslant$62 years), we observed that the G allele were statistically significant associated with advanced disease (OR = 5.1, $P = 0.035$).
Conclusions: Individual differences in cellular microenvironment and in signalling pathways activation may influence cancer development and tumour behaviour. Our preliminary results, suggest that *R497K* functional polymorphism is associated with advanced disease probably because the genetic variant *EGFR 497K* has attenuated functions in ligand binding, growth stimulation, tyrosine kinase activation and induction of proto-oncogenes compared with *EGFR 497R* variant. This genetic profiling may help define higher risk groups and design new target and individualized therapies.

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HIF1a 1772C/T Polymorphism and Prognosis in Renal Cell Carcinoma

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Background: Hypoxia inducible factor (HIF-1) is a key regulator of the genes involved in the cellular response to hypoxia. Overexpression of HIF-1 has been implicated in the pathogenesis of renal cell carcinoma (RCC) and it is argued that polymorphisms of the HIF1A gene may confer susceptibility to RCC. Purpose: To assess the impact of HIF1A functional polymorphism on RCC progression and prognosis.
Material and Methods: The HIF1A 1772C/T (rs11549465) single nucleotide polymorphism was evaluated in a retrospective cohort study of sporadic RCC patients (n = 179) treated at Instituto Português de Oncologia do Porto from 1999 to 2009. Genomic DNA was extracted from peripheral blood samples. Genotyping was performed by Real-Time PCR allelic discrimination method. Recurrence/progression and cancer-specific survival (CSS) were the clinical outcomes studied. The associations of the HIF1A genotypes with clinicopathological prognostic factors and recurrence/progression were analyzed by the chi-square or Fisher tests. Genotypes influencing survival were compared using Cox proportional hazard regression. CSS was estimated by Kaplan–Meier curves and differences were compared using the Breslow test.
Results: None of the genotypes (CC, CT or TT) were significantly associated with ECOG *performance status* (PS), tumour size, tumour extension, Fuhrman grade, lymph node invasion, distant metastasis, TNM stage, histological necrosis or vessel permeation. The T allele was more frequent in patients with ECOG PS 1 than in those with ECOG PS 0 (OR 1.77; 95% CI 0.91–3.40; p = 0.07). The TT genotype and T allele were associated with recurrence/progression (p = 0.042 and p = 0.02, respectively). The CT and CT+TT genotypes were tend associated with unfavorable CSS (HR 2.79; 95% CI 0.88–8.82; p = 0.08 and HR 2.76; 95% CI 0.93–8.22; p = 0.07, respectively). Patients with CT and CT+TT genotypes showed worse CSS than those with the CC genotype (p = 0.012 and p = 0.018, respectively). CSS rates at 5-years were 88.1% vs 83.9% and 76.6% for the CC vs the CT and CT+TT genotypes, respectively.
Conclusion: These results suggest that HIF1A 1772C/T polymorphism may have effects on RCC progression or prognosis, possibly through altered HIF-1 transcription activity.

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INT70/09 Phase II Study of Pazopanib (PZP) Monotherapy for Patients (pts) With Relapsed/refractory Urothelial Cancer (UC) − Updated Results

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Background: Discouraging results have been reported in relapsed/refractory UC with the use of either single-agent or combination therapy (Rx), including targeted Rx. In 2nd line setting, median progression-free (PFS) and overall survival (OS) approximate 3 and 6 months, respectively, then having a dramatic fall in 3rd line and beyond. On 10/2010 we reported preliminary, yet encouraging, results of a phase II trial with PZP, a multitargeted drug with distinct anti-angiogenic activity (ESMO 2010, LBA#23). An update of the trial is presented.
Methods: Eligibility included histologically confirmed UC failing $\geqslant$1 CDDP-based Rx for metastatic disease (perioperative Rx excluded). PZP 800 mg once daily until disease progression or unacceptable toxicity was planned. Both CT scan and PET/CT scan were set at baseline and q4weeks thereafter. An optimal 2-stage Simon's design was applied with the 1st stage recruiting 21 pts and, if $\geqslant$2 responses, a full enrollment of 41 pts. RECIST v.1.1 was used; response-rate (RR) was the primary endpoint.
Results: 36 pts were enrolled from 02/10 to 03/11 (28 males, 8 females). Median age was 64 yrs (42−79). 13 pts (36%) had UC of the upper urinary tract and 23 had a bladder primary tumour. 33 pts had multiple disease sites (median 3, range 1−5). Median number of prior cytotoxic agents was 3 (2−8), of prior Rx lines was 2 (1−4) and median number of prior platinum-based cycles was 5 (2−13). 30 pts (83%) had undergone major surgery, 10 pts had received RT. 30 pts had visceral metastases (hepatic in 17 pts). Median baseline ECOG PS was 1 (0−2). 4 pts (11%) had a confirmed RECIST-defined partial response (PR), 26 had a stable disease (83% clinical benefit). 19 pts (53%) had a clear necrotic evolution of multiple metastases and/or a decreased SUV at PET consistent with PR. Of the 34/36 pts having 2 months minimum follow up, median PFS and OS were 3 months (1−11) and 6 months (2−11), respectively. G3 hypertension occurred in 2 pts while G1−2 asthenia in 13, diarrhoea in 5, anemia and hand-foot syndrome in 3 pts each and G2 increase of liver transaminases in 2 pts. No discontinuations/dose reductions were needed.
Conclusions: Activity and potential efficacy of PZP is demonstrated in very highly pre-treated UC pts. Though the PR-rate by RECIST is low, half of pts had a densitometric/metabolic response, the majority of pts had a clinical benefit and PFS-rate is promising (approaching pure 2nd line results). This is consistent with the mechanism of action of PZP, and highlight the need for new criteria or modifications to existing ones to assess response of angiogenesis inhibitors. Final efficacy and safety outcomes with biomarker analysis will be available in 09/2011 (Cancer.gov registry number: NCT01031875).

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Impact of Targeted Therapies on Muscle Loss and Adipose Tissue in Metastatic Renal Cell Carcinoma (mRCC)

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Background: We previously reported that sorafenib (So) can induce severe muscle depletion (sarcopenia) in RCC. Whether adipose tissue is also involved and whether this phenomenon is due to VEGF inhibition or involves other pathway is unclear. In order to understand the physiopathology of body composition changes with targeted therapies we investigated different drugs, including other VEGF inhibitor (sunitinib [Su]) and mTOR inhibitor (everolimus [E]).
Methods: All patients with mRCC enrolled in 3 previously reported studies: RECORD 1 (E vs placebo [P]), TARGET (So vs. P), and Su continuous dosing were analyzed. Patients were eligible if at least 2 CT scans were available. CT analysis, which has high precision and specificity for evaluation of specific muscles, was used to define change in total skeletal muscle. The 3rd lumbar vertebra was chosen as a landmark. Images were analyzed using Slice-O-Matic software V4.3. Subsequently, tissue cross-sectional areas (cm^2) were computed.
Results: 147 patients (78% male) were evaluable: 36 on E, 37 on So, 36 on Su and 38 on P. Mean durations of treatment were; 136, 172, 142, 117 days respectively on E, So, Su, P. At baseline obesity or overweight were frequent: 42% (P); 55% (E); 55% (So); 66% (Su). Placebo patients had stable body weight (mean$\pm$SD) (+0.9$\pm$3.7 kg), with no changes in muscle mass or adipose tissue. By contrast, patients lost body weight (mean$\pm$SD): −3.5$\pm$5.6 kg, −2.5$\pm$3.8 kg; −3.1$\pm$4.4 kg respectively on E, So, Su. Patients lost skeletal muscle compared with placebo group −3$\pm$8% for E ($p = 0.1$), −5$\pm$8% for So ($p < 0.0001$) and −4$\pm$5% for Su ($p = 0.001$). Interestingly, there were no differences between groups. Muscle loss rate (cm^2/day) was similar for the 3 groups respectively 0.042; 0.045, 0.044 for E; So; Su. No significant changes for adipose tissue were reported: 16$\pm$143% for E; −1$\pm$19% for So; 2$\pm$21% for Su. All combined, after 5 months of treatment, 86 patients were on progressive disease and 33 on stable disease. Loss of adipose tissue but not loss of muscle mass was significantly linked to progressive disease (p = 0.01).
Conclusions: The 3 therapies, everolimus, sorafenib and sutent are responsible for muscle wasting and surprisingly muscle wasting rate is