Some of the panel's preferences and interpretations were seen to be interesting in light of variations from existing Phase III data in some areas. Two such examples were

- Sunitinib or pazopanib or sorafenib were all considered appropriate treatments for patients with metastatic disease who have received prior cytokine therapy
- In nephrectomised patients with metastatic disease and no prior systemic therapy, sunitinib or pazopanib were considered appropriate in all prognostic groups, bevacizumab was considered appropriate only in low/intermediate risk patients and temsirolimus was considered appropriate only in high risk patients.

Conclusions: Differences in opinion could be looked at as areas for further research. Areas where the agreed opinion differs from existing phase III data could have been due to the influence of the results of phase II and other non-randomised studies. Expert opinion may be useful in difficult areas where the data is either absent or sparse. Potential use of this data to generate clinical neural networks that can be used as learning tools is being evaluated.

7115 POSTER DISCUSSION

ABCB-1 and VEGFR-3 Single Nucleotide Polymorphisms (SNPs) and Outcome on Sunitinib (SUN) Treatment in Metastatic Clear Cell Renal Cell Carcinoma (RCC)

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Background: SUN is an oral angiogenesis inhibitor targeting VEGFR-1, -2, and -3, PDGFR-α and -β, RET and c-Kit, approved for the treatment of advanced RCC. Reliable biomarkers predictive for SUN sensitivity or primary/secondary resistance to SUN are lacking.
Methods: We analyzed 15 SNPs in 6 genes (VEGF-A, VEGFR-2, VEGFR-3, CA-9, ABCB-1 and NR-1/3) on 80 fresh frozen clear cell RCC nephrectomy specimens (in 49 patients (pts) on normal kidney tissue, in 31 pts on tumour). After nephrectomy, all the pts were treated in the metastatic setting with SUN as first line anti-angiogenic therapy.
Results: Global median time-to-progression (TTP) was 13.5 months (mo) and global median overall survival (OS) 28.5 mo.
Pts with the TT/TA genotype of the missense rs2032582 SNP (2677G > T or G > A) in the ABCB-1 gene, responsible for drug transport, had a significantly worse outcome than pts with the GT/GA or GG genotypes. TTP was 9.0 versus 16.0 mo ($p = 0.03$) and OS 22.8 versus 31.0 mo ($p = 0.02$) respectively. The TT-variant of the synonymous rs1128503 SNP (1236T > C) was linked to a significantly worse outcome than the CT or CC genotypes. TTP was 9.0 versus 16.0 mo ($p = 0.03$) and OS 22.8 versus 31.0 mo ($p = 0.05$) respectively. No significant link with TTP/OS and the synonymous rs1045642 SNP (3435C > T) in ABCB-1 could be observed.
Pts with the GA variant of the missense rs307826 SNP (1480A > G) in the VEGFR-3 gene, responsible for tumoral angiogenesis and blocked by SUN, had a TTP of 9.3 mo ($p = 0.009$) and an OS of 15.0 mo ($p = 0.009$) versus 18.5 and 31.0 mo for pts with the wild type/wild type AA genotype. For pts with the GT variant of the missense rs307821 SNP (3971G > T), TTP was 10.0 mo ($p = 0.08$) and OS of 15.0 mo ($p = 0.15$) versus 16.0 and 30.7 mo for pts with the wild type/wild type GG genotype.
We did not observe any link between TTP/OS and SNPs in the following genes: VEGFR-2 (rs1870377, rs1870378, rs1870379), CA-9 (rs1538536, rs1934158, rs12553173, the latter a prognostic factor for OS in immunotherapy with interleukine-2), VEGF-A (rs699947, rs2010963) and NR-1/3 (rs4073054, rs2307424).
Conclusions: We observed significant associations between SNPs in genes involved in drug transport (ABCB-1) and in tumoral angiogenesis (VEGFR-3) and response on SUN in advanced clear cell RCC pts.

Poster Presentations (Sun, 25 Sep, 14:00–16:30)
Genitourinary Malignancies – Other

7116 POSTER

Influence of BIRC5 −31G/C Polymorphism in Renal Cell Carcinoma (RCC) Development and Metastization

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Background: Renal cell carcinoma (RCC) is a heterogeneous group of tumours which represents about 3% of all tumours in adults. Furthermore, considering only urological tumours, CCR is the most common tumour after prostate carcinoma and bladder cancer. The mechanism by which a normal cell progresses to a carcinoma, usually involves the disruption of critical molecular pathways, like apoptosis. Alterations in gene expression involved in apoptosis are thus likely to contribute to cancer risk. Survivin, encoded by the *BIRC5* gene, is a multifunctional protein involved in inhibition of apoptosis and regulation of cell cycle. *BIRC5 −31G/C* is a polymorphism in the promoter region, responsible for a G-to-C substitution at −31. This transition has been associated with overexpression of survivin, which may overcome an apoptotic checkpoint and favour aberrant progression of tumour cells through mitosis. Therefore, the purpose of this study was to investigate the role of *BIRC5 −31G/C* polymorphism in RCC development.
Material and Methods: DNA was extracted from peripheral blood cells of 744 individuals: 178 patients with histopathologic diagnosis of RCC and 566 healthy individuals without evidence of neoplasic disease. Genotyping of *BIRC5 −31G/C* polymorphism was obtained by PCR-RFLP. The odds ratio (OR) and its 95% confidence interval (CI) were calculated as a measure of the association between *BIRC5 −31G/C* genotypes and RCC risk.
Results: Statistically significant differences where found between the control and RCC patients groups. Individuals carriers of the CC genotype present a higher risk for RCC development (OR=1.98, 95% CI=1.13–3.49, $p = 0.011$). Stratification according to lymph node metastasis and Fuhrman grade showed that carriers of CC genotype had an increased risk for being diagnosed with lymph node metastasis and higher Fuhrman grade (G1*vs*G2–4) when compared with G allele carriers (OR= 1.89, 95% CI=1.11–3.21, $p = 0.012$; OR=1.77, 95% CI=1.02–3.05, $p = 0.028$, respectively).
Conclusions: Genetic variants in germinal cell line can modulate the cellular microenvironment and consequently influence the molecular mechanism of CCR carcinogenesis. Our results suggest that *BIRC5 −31G/C* genetic polymorphism influence RCC risk and metastasis. This genetic profiling may help to understand RCC behaviour and to define high risk groups and to design new target therapies.

7117 POSTER

Claudins and Ki-67 – Potential Markers to Differentiate Low and High Grade Transitional Cell Carcinomas of the Urinary Bladder

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Background: Updated classification of urothelial cell cancer differentiates low grade and high grade cancers, which determines the potential clinical outcome. However, substantial interobserver variability necessitates new biomarkers to ensure classification. Claudins have been indentified as integral membrane proteins of tight junction strands and their specific expression pattern characterizes normal tissues, different tumour types and defined grades of tumour differentiation. Our aim was to examine expression pattern of claudins and the proliferation marker Ki-67 in low grade and high grade urothelial cell cancers compared with independent control samples of non-tumorous urothelium. Further, to reveal predictive usefulness of claudins.
Materials and Methods: The expression of claudins-1,-2,-3,-4,-5,-7,-10 and Ki-67 was studied with quantitative immunhistochemistry and real time RT-PCR with relative quantification in 103 samples: 86 urothelial cell cancers (27 low grades, 59 high grades) and in 17 non-tumorous urothelia. The results were analyzed regarding overall survival and recurrence-free period as well.
Results: High grade tumours overall showed significantly higher claudin-4 and Ki-67 and significantly lower claudin-7 expression when compared with low grade ones. However, high claudin-7 but not high Ki-67 expression was

significantly associated with shorter recurrence-free survival in non muscle-invasive urothelial cell cancers. Claudin-10 protein was not detected in the samples and only scattered expression of claudin-3 and -5 proteins was found in a few tumour cases.
Conclusions: Claudins and Ki-67 might be used as potential markers to differentiate low grade and high grade urothelial cell cancers, thereby they might enhance the accuracy of pathological diagnosis and might add further information to clinical outcome.

7118 POSTER

Expression of Claudins and Their Prognostic Significance in Non-invasive Urothelial Neoplasms of the Human Urinary Bladder

P. Törzsök[1], E. Székely[1], P. Riesz[2], A. Korompay[1], T. Székely[1], G. Lotz[1], I. Romics[2], J. Tímár[1], Z. Schaff[1], A. Kiss[1]. *[1]Semmelweis University, 2nd Department of Pathology, Budapest, Hungary; [2]Semmelweis University, Department of Urology, Budapest, Hungary*

Background: The members of claudin family are major integral transmembrane protein constituents of tight junctions. Normal and neoplastic tissues can be characterized by unique qualitative and quantitative distribution of claudin subtypes which may be related to clinicopathological features. Differential diagnosis and prognosis of non-muscle invasive tumour entities of urinary bladder epithelium are often challenging.
Objective: To investigate expression profile of claudins in inverted urothelial papillomas (IUP), urothelial papillomas (UP), papillary urothelial neoplasms of low malignant potential (PUNLMP) and intraepithelial (Ta), low grade urothelial cell carcinomas (LG-UCC) in order to reveal potential prognostic and differential diagnostic values of certain claudins.
Patients and Methods: Claudin-1, -2, -4 and -7 protein expressions detected by imunohistochemistry and clinical data were analyzed in 15 IUPs, 20 UPs, 20 PUNLMPs and 20 LG-UCCs.
Results: UPs, PUNLMPs and LG-UCCs showed significantly decreased claudin-1 expression in comparison to IUPs. LG-UCCs expressing claudin-4 over median were associated with significantly shorter recurrence-free survival. PUNLMPs expressing claudin-1 over the median revealed significantly longer recurrence-free survival.
Conclusion: High claudin-1 protein expression might help to differentiate IUP from UPs, PUNLMPs and LG-UCCs. High claudin-4 expression may determine unfavorable clinical course of LG-UCCs, while high claudin-1 expression in PUNLMP was associated with markedly better clinical outcome.

7119 POSTER

NAT1 as a Genetic Predisposing Factor for Urinary Bladder Cancer in Lebanese

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Background: Urinary bladder cancer is the fifth most common cancer in Europe and ranks five in the United States. Historically, the majority of studies investigating bladder cancer focused on oncogenes, tumour suppressor genes, and subsequent cellular events. In the last few years, the role of drug-metabolizing enzymes in bladder cancer has come into focus. Genetic variants of metabolic enzymes are thought to result in critical changes in the metabolism of environmental carcinogens, subsequently altering individual bladder cancer risk. Arylamines, the main carcinogens implicated in bladder cancer, are metabolized by N-Acetyl-Transferases 1 & 2 (NAT1 & NAT2) isoenzymes. The reported NAT1 polymorphism suggests that the NAT1 acetylator genotype may be associated with bladder cancer susceptibility. In Lebanon, the rising incidence of urinary bladder cancer in the past few years is alarming. According to the latest National Cancer Registry report, bladder cancer is currently the second most common malignancy in males (15.1%), almost equal to lung cancer (15.2%). The purpose of this study is to investigate a possible association between NAT1 genotype and bladder cancer risk in a group of Lebanese males.
Materials and Methods: 54 cases and 105 hospital controls were randomly selected for the study from two major medical centers in the city of Beirut. Polymerase Chain Reaction-Restriction-Fragment-Length-Polymorphism (PCR-RFLP) was performed on peripheral blood DNA samples to determine NAT1 genotypes, and an interview-based questionnaire was completed to assess suspected risk factors. The association between bladder cancer and putative risk factors was measured using adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) were derived using a logistic regression analysis. Finally, a gene-environment interaction analysis was applied.
Results: A statistically significant 7 fold increased bladder cancer risk (OR= 7.86, 95% CI: 1.53- 40.39) was observed for individuals carrying at least one NAT1*14A allele. An interaction resulted between occupational exposure to fossil fuel emissions and alleles NAT1*14A and NAT1*10.
Conclusions: Our study provides strong evidence that NAT1*14A allele is a genetic predisposing factor for bladder cancer in Lebanese, and suggests a potential gene-environment interaction. Larger studies are needed to confirm these findings to further investigate the role of NAT1 genotype in bladder cancer etiology.

7120 POSTER

Recurrent Testicular Cancer in a Family With MYH-associated Polyposis

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Background: *MYH*-associated polyposis (MAP) is an autosomal recessive inherited syndrome with similar phenotype to attenuated familial adenomatous polyposis. Biallelic germline mutations in *MYH* predispose individuals to multiple adenoma or polyposis coli. Extraintestinal findings are also noted on occasion; breast, gastric, thyroid and haematological neoplasias as well as sebaceous adenomas and hypertrophy of the retinal pigment epithelium have been described. We report on a family with genetic diagnosis of MAP showing a -previously unreported- recurrent extraintestinal cancer.
Material and Methods: Clinical, pathological and genetic characterization of a family with suspected hereditary colorectal cancer. Lynch syndrome screening analysis was performed by tumour tissue analysis of microsatellite instability (MSI) and immunohistochemical expression (IHQ) of MLH1, MSH2, MSH6 and PMS2 proteins. Germline mutation analysis of the *MYH* gene was performed by sequencing of the entire coding region and the intron-exon boundaries. Co-segregation analysis of the genetic findings in the family was also approached.
Results: The index subject was diagnosed of rectal cancer and multiple adenomatous polyps (n = 8) in right colon at age of 44 yrs. Twelve years before was also diagnosed of testicular embryonal carcinoma. Familial history of cancer revealed a brother diagnosed of testicular embryonal carcinoma at age of 28 yrs and a total of 16 adenomatous polyps at age of 44 yrs. Their father has been diagnosed of few polyps at age of 79 yrs. At least, two different syndromes might be suspected: Lynch syndrome and MAP. The rectal cancer showed normal expression of the proteins analyzed by IHQ, and not MSI was detected. Consequently, Lynch syndrome genetic analysis was disregarded. Therefore, *MYH* gene was tested to confirm the alternative suspicious of MAP and founding two heterozygous variants: [c.317G > A]+[c.1227_1228dup]. Both brothers showed the same genotype, and the genetic analysis of their parents demonstrated that those variants were located *in trans*.
Conclusions: Testicular cancer might be a new extraintestinal manifestation of MAP syndrome. Further analysis to establish the causal relation between *MYH* genetic variants and testicular cancer is underway. A better knowledge of the clinical phenotype of individuals with MAP will make possible the identification and the proper management of mutation carriers in the population at risk.

7121 POSTER

Bladder Preservation a Valid Option for Patients With Muscle Invasive Bladder Cancer − Single Centre Experience

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Introduction: Cystectomy is considered the standard of care for patients with muscle invasive bladder cancer, despite the fact that no randomized studies between cystectomy and radiotherapy or chemoradiotherapy exist (to show superiority of cystectomy). Patients however are often either not fit for cystectomy or do not wish to undergo cystectomy, and hence enter bladder preservation protocols. Here we report our experience in Cyprus with our bladder preservation protocol with all patients treated in the last 10 years.
Methods: 38 consecutive patients with muscle invasive transitional cell cancer were treated with bladder preservation in the last 10 years. Neoadjuvant chemotherapy with 3 cycles of Gemcitabine and Cisplatin, was offered to 20 patients with adequate renal function and performance status. After completion of chemotherapy, there was reassessment with cystoscopy