Results: Age-, tobacco- and body mass index (BMI) - adjusted logistic regression analysis showed an overrepresentation of *LEPR* Gln223Arg Gln homozygous genotype in overall PC cases, compared with controls ($P = 0.040$). Moreover, an earlier onset of disease was verified in *LEPR* Lys656Asn Asn/Asn carriers ($P = 0.049$). Cumulatively, we observed an association between *LEPR* Gln223Arg Arg/Arg carriers and a higher Gleason score ($P = 0.022$). In patients submitted to curative intent treatment, Kaplan-Meier curves and function plots showed a shorter time-to-relapse in *LEPR* Gln223Arg Arg/Arg ($P = 0.006$).
Conclusions: Results from the present study suggest a role for *LEPR* Gln223Arg in PC susceptibility, aggressiveness and in the time-to-relapse. Furthermore, *LEPR Lys656Asn* polymorphism may be a marker of earlier onset of PC. The apparently dual role of LEPR 223 variant, might be due to the higher Arg/Arg binding affinity of LEPR to leptin supporting a peripheral interactome in initiation and a direct effect during development and tumor reactivation. Further studies are warranted to understand the functional role of these variants in leptin pathway activation.

7022 POSTER

Genetic profile of IL-6/IL6R pathway predicts susceptibility, agressiveness and response to hormonal treatment in prostate cancer patients

A. Azevedo[1], R. Ribeiro[1], C. Monteiro[1], V. Cunha[1], N. Francisco[1], A. Fraga[2], F. Pina[3], E. Calais-da-Silva[4], F. Lobo[5], R. Medeiros[1].
[1]Portuguese Institute of Oncology, Molecular Oncology Group, Porto, Portugal; [2]Porto Millitary Hospital, Urology Department, Porto, Portugal; [3]Hospital of S. João, Urology Department, Porto, Portugal; [4]Lisbon Central Hospital, Urology Department, Lisbon, Portugal; [5]Portuguese Institute of Oncology, Urology Department, Porto, Portugal

Background: Interleukin-6 (IL-6), a pleiotropic cytokine with critical roles in inflammation and immune response, seems to be involved in Prostate Cancer (PCa) development and in androgen-independence (AI) mechanisms. Our purpose was to investigate the potential role of functional *IL6* and *IL6R* genetic variants in PCa patients, which have been found to directly affect the *IL6* transcription rate *in vitro* and IL-6 levels *in vivo*.
Material and Methods: We conducted a study in biopsy-proven PCa patients and controls (without malignant cells) ($n = 983$ and $n = 239$, respectively). Genotyping was performed through PCR-RFLP and Real Time-PCR allelic discrimination. Genotypes from *IL6* polymorphisms were individually combined with *IL6R* Asp358Ala polymorphisms according to a functional rationale: Low/intermediate signalling genetic profile and higher signalling gentic profile.
Results: In the *IL6* polymorphism at locus −174 we found an increased risk for C carriers to present a PSA level $\geqslant 20$ ng.mL-1 at the time of diagnosis ($P = 0.02$). Moreover, results show an association of *IL6*−174 C carriers with development of distant metastasis ($P = 0.049$). Carriers of the C allele of *IL6* polymorphism in locus −174 of the promoter region are at higher risk of developing biochemical relapse ($P = 0.035$) and of dying from the disease ($P = 0.008$). Kaplan-Meier survival analysis showed a borderline association of *IL6*−174 C carriers with an earlier AI development ($P = 0.056$). *IL6* −597 A carriers are overrepresented in the group of patients who developed biochemical relapse ($P = 0.013$) and is associated with an earlier onset of PCa development ($P = 0.019$). When *IL6* −174 and *IL6R* polymorphisms were combined, we observed an overrepresentation of higher IL-6 signalling genetic profile in the group of patients with PSA$\geqslant$20 ng.mL-1 ($P = 0.049$), with metastatic disease ($P = 0.049$) and death from cancer ($P = 0.026$). Kaplan-Meier function plots with Breslow test showed an earlier development of AI in higher IL-6 signalling genetic profile ($P = 0.008$).
Conclusions: Functional polymorphism in *IL6* and *IL6R* may contribute to earlier relapse in PCa hormonal-treated patients, supporting the involvement of *IL6*/*IL6R* pathway as an alternative pathway in AI of PCa. Conversely, our results lend support to *IL6*/*IL6R* pathway as an additional therapeutic target during hormonal treatment. The *IL6* and *IL6R* functional polymorphism might be a useful molecular marker for PCa aggressiveness and as a predictive factor for AI relapse.

7023 POSTER

Osteopontin functional genetic polymorphism is associated with prostate cancer biochemical recurrence and androgen independence

R. Ribeiro[1], A. Azevedo[1], N. Francisco[1], C. Monteiro[1], V. Cunha[1], A. Fraga[2], F. Pina[3], F. Calais-da-Silva[4], F. Lobo[5], R. Medeiros[1].
[1]Portuguese Institute of Oncology, Molecular Oncology Group, Porto, Portugal; [2]Millitary Hospital, Urology Department, Porto, Portugal; [3]S. João Hospital, Urology Department, Porto, Portugal; [4]Lisbon Central Hospital, Urology Department, Lisbon, Portugal; [5]Portuguese Institute of Oncology, Urology Department, Porto, Portugal

Background: Understanding the molecular mechanisms that underlie endocrine instigation of indolent tumours may help to clarify several processes in cancer. Elevated osteopontin (OPN) transcription often correlates with increased metastatic potential of transformed cells and have key roles in inflammation and immunity. With the aim to evaluate a genetic variant with functional effect on transcription in *OPN*, we have analysed its association with prostate cancer (PCa) recurrence-free survival and in androgen-independence development.
Materials and Methods: This study was conducted in histologically confirmed PCa patients ($n = 406$). We used Real-Time PCR in order to investigate the genotype and allelic distributions of the polymorphism *OPN* −66 T>G.
Results: Biochemical recurrence risk was significantly associated with OPN functional polymorphism ($P = 0.03$) and Kaplan-Meier function plots analysis with Breslow test showed a lower time to recurrence in G carriers ($P = 0.021$). Furthermore, in those patients submitted to hormonal therapy ($n = 209$), we observed an increased hazard ratio for TT carriers to develop androgen independence (HR = 3.57, 95% CI = 1.5−8.8, $P = 0.005$), after adjustment for relevant prognostic clinical variables.
Conclusions: Results suggest that this functional polymorphism in OPN gene may influence osteopontin expression and therefore instigate the growth of otherwise indolent tumors.

7024 POSTER

Phase Ib dose-finding trial of intravenous (i.v.) panobinostat (PAN) with docetaxel (DOC) and prednisone (PRED) in patients (pts) with castration resistant prostate cancer (CRPC)

U. Vaishampayan[1], D. Rathkopf[2], K.N. Chi[3], S. Hotte[4], N. Vogelzang[5], J. Alumkal[6], M. Agrawal[7], J. Picus[8], A. Fandi[9], H.I. Scher[2]. *[1]Karmanos Cancer Institute, Hematology and Oncology, Detroit MI, USA; [2]Memorial Sloan-Kettering Cancer Center, Oncology, New York City, USA; [3]BC Cancer Agency − Vancouver Cancer Centre, Oncology, Vancouver BC, Canada; [4]Juravinski Cancer Centre, Oncology, Hamilton ON, Canada; [5]Nevada Cancer Institute, Oncology, Las Vegas NV, USA; [6]Oregon Health & Science University, Oncology, Portland OR, USA; [7]Associates in Oncology/Hematology PC, Oncology and Hematology, Rockville MD, USA; [8]Washington University School of Medicine in St. Louis, Oncology, St. Louis MO, USA; [9]Novartis Oncology, Novartis Oncology, Florham Park NJ, USA*

Background: Panobinostat is a potent pan-deacetylase inhibitor that has shown anti-tumor activity in prostate cancer model systems, both in vitro and in vivo, which is potentiated by DOC.
Material and Methods: Open-label, multicenter, dose-finding trial of i.v. PAN given on Days 1 and 8 (10, 15, and 20 mg/m^2) with fixed-dose DOC on Day 1 (75 mg/m^2) and PRED (5 mg bid) in a 21-day cycle in pts with CRPC. All but 3 patients were chemonaive. Pts are required to have adequate organ function and ECOG PS $\leqslant 1$. Pts with cardiovascular abnormalities or QTcF >450ms are excluded. Treatment is continued until disease progression or intolerability. The primary endpoint is determination of maximum tolerated dose (MTD) of i.v. PAN with standard dose DOC using the Bayesian statistical model. Dose-limiting toxicities (DLTs) are defined in Cycle 1.
Results: 27 pts (Cohort 1, $n = 8$; Cohort 2, $n = 10$; Cohort 3, $n = 9$) have been treated, median age of 66 yrs (range 26−88), median Gleason score of 8 (range 7−9), and median PSA of 63.7 ng/mL (range 1.3–672). DLTs included: Gr 4 bradycardia in Cohort 1 ($n = 1$, pt had bradycardia as past medical history) and Gr 4 neutropenia resulting in Day 8 PAN dose omission ($n = 2$, Cohort 2; $n = 1$, Cohort 3). The MTD has not been reached. The maximal dose of PAN allowed by the protocol is 20 mg/m^2. Gr 3/4 adverse events included: neutropenia (19 pts), febrile neutropenia (7 pts), syncope (2 pts), DVT (2 pts). Gr 3 or 4: fatigue (1 pt) and no thrombocytopenia, or diarrhea have been reported. Among the 891 ECGs performed, 2 pts had QTcF increase >60ms from baseline, with no QTcF >480ms reported. In Cohorts 1 and 2, the median number of cycles was 6; 2 pts in Cohort 1 received $\geqslant$15 cycles and 5 pts in Cohort 2 received $\geqslant$6 cycles. In Cohorts 1 and 2, 10 pts had PSA declines, 7 of whom had a >50% decline in