7018 POSTER

Alpha-emitting Radium-223: two years follow up from a randomized phase II study in patients with bone metastases from hormone refractory prostate cancer

S. Nilsson[2], L. Franzen[3], C. Parker[4], B. Bolstad[5], T. Ramdahl[5], M. Thuresson[6], O. Bruland[1]. *[1]The Norwegian Radium Hospital, Oncology, Oslo, Norway; [2]Karolinska University Hospital, Oncology, Stockholm, Sweden; [3]Sundsvall Hospital, Oncology, Sundsvall, Sweden; [4]Royal Mardsen Hospital, Oncology, Sutton, United Kingdom; [5]Algeta ASA, Clinical Department, Oslo, Norway; [6]Statisticon AB, Clinical Department, Uppsala, Sweden*

Background: The bone-seeking pharmaceutical Alpharadin® ($^{223}RaCl_2$) is under clinical development as a novel treatment for patients with skeletal metastases. Clinical studies have shown that toxicity is low, repeated dosing is feasible and seems to improve overall survival. [1] A pivotal phase-3 trial in patients with hormone refractory prostate cancer (HRPC) is currently recruiting.
Material and Method: In a randomized phase 2 trial 64 HRPC patients with painful bone metastases received 4 monthly injections of Alpharadin (A) or placebo (P) as an adjuvant to external beam radiotherapy (EBRT). A 4.5 months difference in survival was observed at 18 months follow up. Here we report 24 months follow up data on survival, long term toxicity, subgroup analyses based on disease status at inclusion and pre-treatment EBRT.
Results: At 24 months, ten patients (30%) that received A were alive and four (13%) in the P-group. Median survival was 65 weeks compared with 46 weeks, respectively (ITT). Hazard ratio adjusted for baseline covariates was 2.10 (95% CI; 1.140−3.88; p = 0.017, Cox regression). The median survival was more than 40% longer in the A group at all levels of extent of disease (EOD = number of "hot-spots": 20; super-scan). The largest absolute difference occurred in patients with lowest EOD; 107 weeks for A and 68 weeks for P. For all patients who received four injections (28 patients in A, 21 in P), the median survival was 93 and 49 weeks (p = 0.043, Log-rank). In a composite analysis of patients with Hb > 110, bone-ALP
Conclusions: The therapeutic benefit seems to be greater for more fit patients than for those with extensive skeletal involvement. However, the relative improvement in survival was maintained irrespective of extent of disease at baseline. A benign side effect profile was documented following repeated Alpharadin® treatment.

References

[1] Nilsson S, et al., Lancet Oncology 2007

7019 POSTER

Vaccination with Survivin and PSMA-derived peptides: results of a pilot study in prostate cancer patients failing radiotherapy or surgery

L. Rivoltini[1], S. Villa[2], A. Marrari[3], P. Squarcina[1], P. Filippazzi[1], R. Salvioni[4], T. Rancati[5], M. Asioli[1], G. Parmiani[6], R. Valdagni[5]. *[1]Fondazione IRCCS Istituto Nazionale Tumori, Department of Immunotherapy of Human Tumors, Milano, Italy; [2]Fondazione IRCCS Istituto Nazionale Tumori, Department of Radiotherapy, Milano, Italy; [3]Fondazione IRCCS Istituto Nazionale Tumori, Department of Medical Oncology, Milano, Italy; [4]Fondazione IRCCS Istituto Nazionale Tumori, Department of Urology, Milano, Italy; [5]Fondazione IRCCS Istituto Nazionale Tumori, Prostate Program, Milano, Italy; [6]Ospedale San Raffaele, Department of Immuno-Biotherapy of Melanoma and Solid Tumors, Milano, Italy*

Background: A significant number of patients (pts) progress after prostate cancer (PCa) first line treatments. Among the new experimental approaches utilized to reduce the risk of recurrence anti-tumor vaccines (vax) might be a promising strategy. Preliminary results of a multiple peptide-based pilot study are here presented.
Methods: A phase I-II vax trial with HLA-A·0201-restricted peptides from PSMA and Survivin was carried out in 20 pts with b-failure after radiotherapy (RT) or surgery (8 radical RT, 8 salvage RT and 4 prostatectomy). Mean pre-vax PSA was 1.83 ng/ml, mean pre-vax PSA doubling-time was 1yr (range 1mo−2.5yrs). Vax consisted of two peptides from PSMA (PSMA4−12 and PSMA711−719) and one from Survivin (SVV96−104/97M) emulsified in Montanide ISA 51 and given by 4 fortnightly (priming) and 4 monthly administrations (boosting). To selectively eliminate regulatory T cells (Treg) and possibly enhance immunization, peptides were preceded by low dose cyclophosphamide (CTX, 300 mg/mq, i.v.). Extensive monitoring of antigen-specific T cell responses in peripheral blood (by IFNγ Elispot, HLA-A·0201/peptide multimer staining and short-term in vitro cultures) and analysis of CTX effect on CD4+CD25+Foxp3+ Treg frequency were performed. PSA trends were also analysed.
Results: Vax was well tolerated. According to Elispot more than 90% treated pts developed a statistically significant increase in the frequency of CD8+ T cells recognizing PSMA711−719 (8±11 in pre-vax vs 79±28 in post-vax) or SVV96−104/97M (pre:11±12 vs post:160±42) peptides, while poor immunogenicity was observed with PSMA4−12. No effect of CTX on Treg frequency was instead observed. 6/20 pts showed no biochemical response to vax and were switched to hormonal therapy, while 14/20 exhibited a significant, though transient PSA decrease during vax (11 in the priming and 3 in boosting phase).
Conclusions: Peptide vax seems to rapidly enhance specific immune responses in most pts, resulting in a significant decrease of PSA levels in 70% pts. However the antigenic stimulus provided by immunization is suboptimal, causing a transient effect on PSA and requiring continuous vaccinations to be maintained. Vax might help to postpone the prescription of hormonal therapy in the absence of major side effects, but immunization protocols inducing efficient tumor cell killing still need to be identified.

7020 POSTER

Performance status and interval from first-line docetaxel-based chemotherapy to progression are significant prognostic factors in patients with castration-resistant prostate cancer receiving second-line chemotherapy

Y. Loriot[1], C. Massard[1], M. Gross-Goupil[1], T. De La Motte Rouge[1], A. Bossi[2], B. Escudier[1], A. Chauchereau[3], K. Fizazi[1]. *[1]Institut Gustave Roussy, Department of Medicine, Villejuif, France; [2]Institut Gustave Roussy, Department of Radiotherapy, Villejuif, France; [3]Institut Gustave Roussy, Prostate Cancer Translational Research Unit, Villejuif, France*

Background: No established second-line chemotherapy is currently validated in patients with metastatic castration-resistant prostate cancer (CRPC) previously treated with docetaxel. However, a number of these patients commonly receive second-line chemotherapy. We investigated the influence of clinico-pathologic factors on the survival of 61 patients with CRPC who received second-line chemotherapy.
Methods: Between January 2004 and December 2006, 61 patients with CRPC were given second-line chemotherapy after failure of docetaxel-based chemotherapy. This study analyzes the correlation between clinical factors evaluated at the time of second-line and the overall survival in these patients using univariate and multivariate analysis.
Results: Sixty-one patients with CRPC were given second-line chemotherapy after first-line docetaxel-based chemotherapy. Second-line chemotherapy consisted of carboplatin-etoposide (n = 42), docetaxel (n = 8), mitoxantrone (n = 4), doxorubicin (n = 3), oral etoposide (n = 2), vinorelbine (n = 1) and cyclophosphamide (n = 1). In univariate analysis prognostic factors for overall survival included performance status (PS) (p < 0.001), interval from first-line chemotherapy to progression (p < 0.001) and median serum PSA (p = 0.1). Multivariate analysis identified PS (hazard ratio (HR), 0.26; 95% CI, 0.09−0.81; P < 0.02) and PFS to first-line chemotherapy (HR, 2.45; 95% CI, 1.2−4.8; P < 0.01) as the independent prognostic factors for overall survival.
Conclusions: Both PS and interval from the first-line docetaxel-based chemotherapy to progression are independent prognostic factors for overall survival in patients with CRPC treated with second-line chemotherapy. This analysis suggests that some easily available clinical factors may help to select patients with CRPC who may benefit from second-line chemotherapy. These both factors should be used as stratifications factors in future clinical trials.

7021 POSTER

Leptin receptor genetic variants are associated with prostate cancer development, aggressiveness and the time to biochemical relapse

C. Monteiro[1], R. Ribeiro[1], A. Azevedo[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: Leptin is a hormone synthesized in fat cells with a relevant role in cell proliferation and angiogenesis. Its receptor (LEPR) was found in human normal prostate and prostate cancer cells (PC), while recent *in* vitro and *in vivo* studies demonstrated a role of leptin/LEPR pathway in androgen-independence mechanism. Our purpose is to understand the role of 3 non-synonymous *LEPR* polymorphisms (Gln223Arg, Lys656Asn and Lys109Arg) in PC risk, aggressiveness and in biochemical relapse.
Methods: We genotyped the *LEPR* polymorphisms in biopsy confirmed PC patients (n = 602) and controls with absent malignant neoplasia (n = 209) by PCR-RFLP and Real-time PCR.

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