PSA from baseline. In Cohort 3, 7 of 9 pts are still on treatment after 2 cycles, with 1 patient having a 99% PSA reduction at Cycle 4. Of the 13 pts enrolled with measurable disease, 2 pts have achieved an unconfirmed partial response and 6 pts have unconfirmed stable disease using RECIST criteria.
Conclusions: The maximal dose of panobinostat allowed by the protocol in combination with docetaxel and prednisone is 20 mg/m^2. The combination is well tolerated and has shown promising activity both for PSA reduction and tumor shrinkage. The combination warrants further exploration in a randomized Phase II setting.

7025 POSTER

Prognostic value of hypermethylation for retinoic acid receptor beta (RARB) and p-16 genes in patients with prostate cancer

A. Ameri[1], M.H. Emranpour[1], M.R. Abbaszadegan[2], A. Alidoosti[1], F. Taslimi[1], K.H.M. Sheibani[1]. [1]*Imam Hossein Hospital, Radiation oncology, Tehran, Iran;* [2]*Mashhad University of Medical Sciences, Bu-Ali Research Institute, Mashhad, Iran*

Background: Correlations between specific gene hypermethylation and clinicopathologic features suggestive of aggressive disease characteristics indicate that these genes may have prognostic potential. Such molecular markers may help to identify men who will undergo recurrence, so that they can be targeted for more aggressive therapy. we investigated hypermethylation of promoter genes, retinoic acid receptor β (RARB) and p-16, prostate cancer patients with different prognostic features who referred to three hospital in Iran between Jan 2007 and April 2008.
Methods: 63 prostate biopsy specimens from three different groups of patients, 21 benign prostate hyperthrophy (BPH) as control group, 21 prostate cancer who had good prognostic features, and 21 patients with poor prognostic feature were evaluated. The prostate biopsy specimen examined for hypermethylation of promoter genes RARB and p-16 with Methylation Specific PCR (MSPCR) and odds ratio for any association with patients' prognosis were tested by Chi-square and Fisher exact test.
Results: There was no RARB methylation in BPH specimens. In patients with good prognostic features 7 (33.3%) were positive for RARB methylation which was significantly more common than control group ($p < 0.000001$).RARB methylation was found in 15 (71.4%) of patients specimens with poor prognostic features, that were more common than control group (0.000001). The RARB methylation in patients with poor prognostic factors were significantly more common than in patients with good prognostic features ($p < 0.02$). There was no p-16 positive subject in BPH group. In patients with good prognostic features 19% had methylation of p-16 and of those with poor prognostic features 47.6% were positive for RARB methylation. The P16 methylation in patients with poor prognostic factors were significantly more common than in patients with good prognostic features($p < 0.00001$).
Conclusion: Methylation of RARB and p-16 are good indicator for early detection and predicting prognosis of prostate cancer in Iranian patients.

7026 POSTER

Deriving prostate alpha-beta ratio using carefully matched groups, long follow-up and the Phoenix definition of biochemical failure

R. Shaffer[1], T. Pickles[2], R. Lee[3], V. Moiseenko[3]. [1]*Imperial College NHS Trust, Radiotherapy, London, United Kingdom;* [2]*British Columbia Cancer Agency, Radiotherapy, Vancouver, Canada;* [3]*British Columbia Cancer Agency, Physics, Vancouver, Canada*

Background: Prior studies derived a low value of a/β for prostate cancer (e.g. 1−2 Gy) using outcome data from external beam radiotherapy (EBRT) and permanent prostate brachytherapy (PPB). However, these values are associated with wide confidence intervals and inaccuracies such as poorly-matched groups, differing definitions of biochemical failure and insufficient follow-up.
Materials and Methods: Patients with Canadian Consensus Risk Group low- or low-tier intermediate risk prostate cancer, treated with either EBRT or PPB, were matched for PSA, Gleason score, T-stage, percentage of positive cores, androgen deprivation therapy duration and era, yielding 118 pairs. The Phoenix definition of biochemical failure was used. The best value for a/β was found using maximum likelihood analysis, and 95% confidence intervals using the profile likelihood method. The linear quadratic formalism was applied with radiobiological parameters set at RBE = 1, Tpot = 45 days, and repair half-time = 1 hour. Sensitivity analysis was performed using extreme values of these parameters.
Results: PPB and EBRT groups were well-matched with respect to all known risk factors. Median follow-up or time to failure was 60 months. Kaplan-Meier estimates of freedom from biochemical failure (bNED) showed superiority of PPB compared to EBRT (log-rank test $p = 0.001$): Estimates of probability of bNED were 82% and 95% at 72 months for EBRT and PPB; and 63% and 95% at 90 months. The value of a/β that best fitted the outcome data was >30 Gy, with a lower 95% confidence limit of 3.2 Gy. This was confirmed on bootstrap analysis. Varying the parameters to extreme values yielded a best-fit a/β of at least 3.0 Gy.
Conclusions: Our result of >30 Gy as the best estimate of a/β for low and low-intermediate risk prostate cancer directly contrasts with prior best estimates of 1−2 Gy. Obtained values of a/β result from superior outcomes for PPB observed for long follow-up time. If the true value of a/β is not less than the rectal a/β then radiation hypofractionation may not improve the therapeutic ratio.

7027 POSTER

Interim results of a phase II trial of oxaliplatin and pemetrexed as 2nd/3rd line therapy in castration resistant prostate cancer (CRPC)

T.B. Dorff[1], S. Groshen[1], D.D. Tsao-Wei[1], A. Goldkorn[1], C. Korn[1], D.I. Quinn[1], J. Pinski[1]. [1]*University of Southern California, Medical Oncology, Los Angeles, USA*

Background: There is no standard of care for men with metastatic CRPC after disease progression on docetaxel. Pemetrexed and oxaliplatin have each shown modest single-agent response rates in CRPC and have non-overlapping toxicities; this trial evaluates their efficacy in combination.
Methods: Men with CRPC whose disease progressed on docetaxel were eligible. A two-stage design ($\alpha = 0.1$, $\beta = 0.1$) was used to determine the response rate as primary endpoint (RECIST, or PSA if no measurable disease present); 47 patients are planned. After giving written informed consent, 31 men enrolled from July 2006 - November 2008. Treatment was pemetrexed 500 mg/m^2 IV and oxaliplatin 120 mg/m^2 IV every 3 weeks, with folate and B12 supplementation.

Response	Number (%)
Overall (N = 31)	
PR (>50% decrease PSA or RECIST)	10 (32%)
SD	12 (39%)
PD	6 (19%)
Inevaluable – off treatment	4 (13%)
RECIST (N = 26)	
PR	4 (15%)
SD/unconfirmed PR	18 (58%)
PD	4 (13%)
Inevaluable	5 (16%)

Toxicity	Grade 1/2	Grade 3/4
Allergic	7	1
Auditory	12	0
Bone Marrow	22	8
Constitutional	22	6
Dermatologic	5	0
Gastrointestinal	24	0
Hemorrhage	5	0
Hepatic (including alk phos)	23	4*
Metabolic/Laboratory	12	0
Neurologic (dizziness, confusion, ataxia)	18	5
Pain	7	3
Pulmonary	2	1
Renal	4	0

*2 grade 3 AST/ALT

Results: Median age was 66 (41−81), 72% were Caucasian and 97% had ECOG performance status 0−1. Median baseline PSA was 286 ng/mL (range 4.8−2290). All had metastatic disease with 1 (55%) or 2 (45%) prior chemotherapy regimens; 94% had bone involvement. Subjects received a median of 6 treatment cycles (range 1−21); 3 continue on study. Responses are summarized in the table; 8 of the 31 patients (26%) have achieved a PSA response, and 4 objective PRs by RECIST, out of 26 evaluable patients. Eighteen (58%) had stable disease. After 15 deaths, median survival is 11.8 months (95% CI 7.5−23.5+). Toxicities are presented in the table; the only grade 4 event was thrombocytopenia. Common grade 3 events included fatigue (6 subjects), hematologic (7), and neurologic (5). Two patients died while on study, one due to disease progression and the other one due to cardiopulmonary arrest.

Conclusion: These data suggest safety and promising efficacy of oxaliplatin and pemetrexed for 2nd and 3rd line treatment of CRPC, with a majority of patients achieving stable disease or better.

7028 POSTER

Dasatinib and docetaxel combination treatment for patients with metastatic castration-resistant prostate cancer (CRPC): analysis of Study CA180−086

J. Araujo[1], P. Mathew[2], A.J. Armstrong[3], E.L. Braud[4], E. Posadas[5], M. Lonberg[6], G. Gallick[7], G.C. Trudel[8], P. Paliwal[9], C.J. Logothetis[1]. *[1]University of Texas M.D. Anderson Cancer Center, Genitourinary Medical Oncology, Houston, USA; [2]Tufts University, School of Medicine, Boston, USA; [3]Duke Comprehensive Cancer Center, Departments of Medicine and Surgery, Durham, USA; [4]Springfield Clinic, Hematology and Oncology, Springfield, USA; [5]University of Chicago, The University of Chicago Medical Center, Chicago, USA; [6]Hematology Oncology Associates of Rockland, Department of Clinical Research, New York, USA; [7]University of Texas M.D. Anderson Cancer Center, Department of Cancer Biology, Houston, USA; [8]Bristol-Myers Squibb, Oncology Global Clinical Research, Wallingford, USA; [9]Bristol-Myers Squibb, Biostatistics, Wallingford, USA*

Background: SRC and SRC-family kinases (SFK) play a key role in proliferative, invasive, and bone-metastatic processes in solid tumors. Dasatinib (Bristol-Myers Squibb) is a potent SRC and SFK inhibitor that inhibits prostate cancer cell proliferation and migration *in vitro*. In clinical studies, dasatinib treatment was associated with downregulation of osteoclast activity and bone turnover. Following preliminary reports from Study CA180−086 (ASCO 2009, abs. 5061), we report an intent-to-treat analysis for dasatinib and docetaxel combination treatment 5 months after completion of accrual.
Methods: CA180−086 is a phase 1/2 study in men with CRPC progressing despite castrate levels of testosterone (⩽50 ng/dL) and requiring chemotherapy. Patients (pts) (phase 1) received dasatinib 50–120 mg once daily (QD) and docetaxel 60−75 mg/m^2 every 21 days (Q21D), with selected doses of dasatinib 100 mg QD plus docetaxel 75 mg/m^2 Q21D and prednisone 5 mg twice daily administered to all pts enrolled in phase 2. Bisphosphonate continuation was permitted but anti-androgens were discontinued. Responses were determined according to PSWG2 criteria. To assess bone turnover, urinary N-telopeptide (uNTX) and serum bone alkaline phosphatase (BAP) levels were measured.
Results: At the time of analysis, median treatment duration was 4.8 mos (range 0.1−9.6) and 18/46 treated pts remain on therapy. The most common grade 1/2 adverse events (AEs) were fatigue, dysgeusia, and GI and skin disorders. A grade 3 AE was reported in 9 pts and a grade 4 AE in 2 pts. A prostate-specific antigen (PSA) response was observed in 21/43 evaluable pts (49%). Bone scans showed reduction in size and number of lesions in 11/39 (28%) pts and stable lesions in 27 (69%) pts (n = 8 at ≈6 wks; n = 6 at ≈12 wks; n = 6 at ≈18 wks; n = 5 at ≈24 wks; n = 2 at ≈30 wks). Of 31 pts with RECIST-evaluable lesions, best response was: partial response (PR) in 14; unconfirmed PR in 4 (still on study); stable disease in 12 (6−21 wks); and progressive disease in 1 pt. Of pts evaluated for bone markers, 17/34 (50%) had a ⩾35% uNTx decrease (2 received bisphosphonates) and 24/32 (75%) had a BAP decrease from baseline (9 received bisphosphonates).
Conclusions: Dasatinib and docetaxel treatment is well tolerated. These promising data, showing modulation of bone markers and PSA at a higher-than-expected rate, support combined anti-tumor and anti-osteoclast targeting and serve as the basis for the ongoing phase 3 study of this combination.

7029 POSTER

CYP17 gene polymorphism in prostate cancer

M. Sivonova[1], D. Dobrota[1], T. Matakova[1], P. Racay[1], J. Hatok[1], J. Kliment[2]. *[1]Jessenius School of Medicine, Department of Medical Biochemistry, Martin, Slovak Republic; [2]Jessenius School of Medicine, Department of Urology, Martin, Slovak Republic*

Background: The cytochrome P450c17a mediates both steroid 17a-hydroxylase and 17, 20-lyase activities and functions at key steps in the genesis of human sex steroid hormones. The 5′-untranslated promoter region of the *CYP17* gene contains a polymorphic T-to-C substitution that gives rise to *A1* (T) and *A2* (C) alleles. The *CYP17* polymorphism may play a crucial role in the etiology of hormone-related cancers such as prostate cancer and breast cancer. The aim of our study was to investigate the distribution of the *CYP17* genotype between a control group and prostate cancer patients.
Material and Methods: Blood samples from 200 subjects (mean age 59.5±7.4 years, range 50 - 78 years) were obtained from healthy, unrelated subjects. A total of 195 prostate cancer patients (mean age 67.0±8.2 years, range 50−85 years) with histologically verified prostate cancer were invited to participate in the project. Both patients and controls were interviewed regarding age, smoking habits, drinking habits, possible chemical exposure, previous and/or current prostate diseases, incidence of cancer and chronic diseases. PCR-RFLP (polymerase chain reaction-restriction fragment length polymorphism analysis) was used to detect *CYP17* polymorphisms. The χ^2 method was used to test frequencies of genotypes/allele in prostate cancer patients and controls.
Results: The frequency of the *A2* allele was similar in cases and controls. Compared with men with the *A1*/*A1* genotype, the adjusted odds ratio was 1.06 (95% CI = 0.68 to 1.64) for the *A1*/*A2* and 0.66 (95% CI = 0.37 to 1.20) for the *A2*/*A2* genotype. The multivariate analysis confirmed the association between PSA levels and *CYP17* genotypes (*A1*/*A1 vs. A1*/*A2; A2*/*A2*). Prostate cancer patients with PSA levels (4−10 ng/ml) and *A1*/*A2; A2*/*A2* genotypes had an excess risk to develop prostate cancer (OR = 2.84, 95% CI = 1.06 to 7.62; OR = 3.15, 95% CI = 0.75 to 13.3, respectively).
Conclusions: These results suggest that the *CYP17 A1*/*A2* and *A2*/*A2* genotypes predict susceptibility to prostate cancer in men with serum PSA levels above 4 ng/ml. It is also possible that *CYP17* interacts with other genes that influence risk of prostate cancer.
Acknowledgements: This work was supported by grants MH SR 2007/45-UK-10, MH SR 2007/57-UK-17, UK/264/2006, MVTS Bil/CR/SR/UK/06 and AV 4/0013/05.

7030 POSTER

Dose finding and safety analysis of inecalcitol in combination with docetaxel-prednisone regimen in hormone-refractory prostate cancer (HRPC) patients (pts)

J. Medioni[1], G. Deplanque[2], T. Maurina[3], J.M. Ferrero[4], J.M. Rodier[5], E. Raymond[5], J. Allyon[1], S. Kalla[2], J.F. Dufour-Lamartinie[6], S. Oudard[1]. *[1]Hôpital Européen Georges Pompidou, Oncology, Paris, France; [2]Centre Hospitalier St Joseph, Oncology, Paris, France; [3]Centre Hospitalier Universitaire Jean Minjoz, Oncology, Besançon, France; [4]Centre Antoine Lacassagne, Oncology, Nice, France; [5]Hôpital Beaujon, Oncology, Clichy, France; [6]Hybrigenics, Oncology, Paris, France*

Introduction: Inecalcitol is a novel synthetic vitamin D3 analogue with potent antiproliferative effects in human cancer cell lines and a 100-fold lower hypercalcemic activity than calcitriol in animal models.
Methods: In this study, escalating dosages of inecalcitol was combined to chemotherapy in naive HRPC pts. Safety and efficacy were evaluated in groups of 3−6 patients receiving inecalcitol daily or every other day on a 21-day cycle in combination with docetaxel (75 mg/m^2 q3w) and oral prednisone (5 mg bid). Biphosphonates were prohibited during the first cycle. Patients received up to six cycles unless unacceptable toxicity or disease progression. Primary endpoint was dose limiting toxicity (DLT) defined as grade 3 hypercalcemia within the first cycle. Calcemia, creatininemia and CBC were assessed weekly; biochemistry, ECG and PSA every 3 weeks. Efficacy endpoint was PSA response defined as ⩾30% decline within 3 months.
Results: Five dose levels: 40, 80, 160, 300, 600 μg have been evaluated in 34 pts; 9 pts are still being treated at 600 μg; 25 pts have completed 6 cycles (13 bone metastases; 3 extrasqueletic metastasis, 8 bone and extrasqueletic metastases; 1 PSA-only disease). Median age was 72 years [range 53−87], median Gleason score (Gs) 7 [36% Gs 10−8, 64% Gs 7−6] and median PSA 41.5 ng/mL [range 0.9−962.4]. No increased calcemia was reported. Most adverse events (AE) were G1−2, asthenia (19pts), constipation (14pts), diarrhea (13pts). G3−4 AEs were neutropenia (11pts) lymphopenia (9pts), asthenia (3pts), arrhythmia (2 pts), general health deterioration (2pts) and diarrhea (1pt). None of these AEs was considered related to inecalcitol. Of the 23 evaluable pts for PSA response, 20 (87%) had ⩾30% PSA decline.
Conclusion: Results from this ongoing study show the safe toxicity profile of inecalcitol when given daily in HRPC pts. PSA responses with this combination are encouraging. As DLT was not reached, higher dose of inecalcitol (1000 μg/day) are being tested.

7031 POSTER

The impact of neoadjuvant and concurrent MAB for intermediate & high risk localized prostate cancer treated with IMRT

K. Hatano[1], M. Sakai[1], H. Araki[1], T. Imagunbai[1], N. Tohyama[1], T. Kodama[1], T. Kojima[1], K. Ueda[2], M. Maruoka[2]. *[1]Chiba Cancer Center, Radiation Oncology, Chiba, Japan; [2]Chiba Cancer Center, Urology, Chiba, Japan*

Background: The sensitivity to hormonal therapy in Japanese prostate cancer patients is though to be much higher than that in other countries.