prostate or moderate to high risk disease. Neoadjuvant hormonal therapy (NHT), while well studied in patients receiving external beam radiotherapy, has not been adequately assessed in the implant patient.

Methods: 151 men with T1-T2 prostate cancer were treated with 6 months of LHRH agonist plus an anti-androgen (3 months prior to and 3 months after implant) in conjunction with either I-125 (160 Gy) or Pd-103 (124 Gy) seeds. There were 76 (50.3%) with PSA < 10 ng/ml, 58(38.4%) with PSA >10-20 and 17(11.3%) with PSA > 20 ng/ml. Clinical stage was T2a or less in 76 and 100 (66.2%) had a Gleason score < 6. 35/151 (23.2%) were treated with NHT because of prostate size > 50 cc while the rest received NHT because of presenting PSA > 10 ng/ml, stage > T2a or Gleason > 6. Median follow up was 4 years (range 2-9.5 years). PSA failure was calculated with actuarial methods using 3 consecutive rises (ASTRO definition) or a PSA > 1.0 ng/ml.

Results: Of the 151 patients, 17 (11.3%) experienced a PSA failure. The six-year likelihood of being free from PSA failure was 88%. The 6-year PSA freedom from failure rate for patients with a PSA < 10 was 95%, PSA >10 to 20 was 86% and PSA > 20 was 69% (p=0.01). A similar benefit was seen for those with PSA < 15 vs > 15 (91% vs 78%, p=0.04). Gleason score did not influence outcome, with 89% free of failure vs 86% (p=0.5) for 6 or less vs score 7 or greater. There was a trend to improved outcomes for lower stage patients; with stage T2a or less 92% free of failure vs 84% (p=0.07) in higher stage patients.

Conclusion: Low risk prostate cancer patients (PSA < 10 ng/ml) who present with large prostates and require NHT to downsize the gland have an excellent (95%) freedom from PSA outcome following permanent brachytherapy. Intermediate risk patients presenting with a PSA < 15 can also be successfully managed with 6 months of hormones plus seed implantation. This 6-month NHT/brachytherapy regimen, which has been found to preserve potency in 70% of men (Stock et al. J. Urol. 165:436, 2001), should be considered an effective treatment option for these two groups. High risk patients (PSA > 15) might further benefit with the addition of external beam irradiation or longer hormonal therapy treatment.

575 ORAL

Diethylstilbestrol (DES) in hormone resistant prostate cancer (HRPC): PSA response, palliative benefit and survival

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The use of DES as first line treatment of advanced prostate cancer has declined due to thromboembolic side effects. The precise mechanism of its activity in HRPC remains controversial, but suggestion of a direct cytotoxic effect led us to explore its use in HRPC. We report our experience with DES in patients failing androgen suppression. We have treated a total of 243 patients (median age: 72; range: 45-93) with advanced PC after failing androgen suppression (LHRHa or orchidectomy) with DES between August 1992 and August 2000. 189 patients had metastatic and 54 patients locally advanced disease. Median time since initial hormonal treatment was 30 months (2.3-161). Median number of previous hormonal manoeuvres was 2 (1-6), antiandrogens if used were withdrawn >1 month before DES with subsequent biochemical or clinical progression. Median pre-DES PSA was 258 ng/ml. DES (1mg: 127 patients; 3mg: 115 patients) plus low dose aspirin (75 mg) was given following breast bud radiotherapy (8 Gy). Median treatment duration was 3.4 months. Some fall in PSA was seen in 77.5% of men. PSA response of >50% compared to baseline confirmed on 2 measurements at least 3 weeks apart, was seen in 29.1% of patients (1 mg: 26.1%; 3 mg: 32.4%). 17% had a partial response and 38% stable disease according to NPCP criteria. Of patients with bone pain, 33% had a more than 1 point and 14% a more than 2 point decline in EORTC pain score. Median time to biochemical progression was 4.6 months. Median survival was 9.6 months [1 year: 38.9% (3.2-45.6); 2 year: 15.5% (10.2-21.8)]. Survival was significantly better in patients with >50% reduction in PSA (p<0.0001). Thromboembolic complications were seen in 11% of all patients. DES at 1 or 3 mg daily can give useful palliative responses equivalent to chemotherapy after failure of standard hormonal therapy in HRPC. The degree of PSA fall correlates with survival.

576 ORAL

Comparison of real time intra-operative dosimetry to post-implant ct control: a multicenter study of prostate brachytherapy quality outcomes:

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Purpose: Permanent seed implantation has become a popular treatment option for localized prostate cancer. The goal of the implant should be to deliver 140 Gy or greater to 90% of the prostate gland (D90) in all cases. Two implant methods available are the pre-plan technique and the ProSeed method, which utilizes intra-operative dose adjustment to optimize dose calculations. This study evaluated the initial experience of the first 5 European centers to perform the ProSeed method.

Methods: Data from 132 patients with stage T1-T2 prostate cancer who were treated by iodine-125 implantation from July 1,2000 to August 20, 2001 was analyzed. Peripheral needles and seeds were placed according to rules previously developed for this technique. After needle placement, US images were acquired into a modified treatment planning system (VariSeed 6.7) and actual needle and seed positions were registered. Interior needles and seeds were placed according to dose optimization rules as determined by the planning computer. Quality control was taken one month later from CT images. Doses to 95% and 90% of the prostate (D95 and D90), 30% of the urethra (U30) and the volume (cc) of rectum covered by 160 Gy (VR 160) for the real time intra-operative dosimetry (RTP) were compared (t-test) to the CT dosimetry (PID) results.

Results: Median patient age was 66 years (range 51-76), median PSA was 9 ng/ml (range 3.9-35) and median Gleason score was 5 (range 2-7). Mean prostate volume prior to needle placement was 40.7 cc (range 10-72), after needle placement at time of image capture was 42.9 cc (range 22-72, p=0.264) and for CT dosimetry was 52.3 cc (range 33-73, p=0.09). Dosimetry results were as follows for RTP vs PID respectively: the mean D95 were 176 vs 162 (min 150 vs 125, max 203 vs 202, p=0.0007), the mean D90 were 187 vs 184 (min 165 vs 140, max 231 vs 240, p= 0.28), the mean U30 were 199 vs 257 (min 165 vs 190, max 265 vs 318, p= 0.00003), and the mean VR160 were 0.617 vs 1.05 (min 0 vs 0.01, max 3.82 vs 2.91, p=0.78) respectively.

Conclusions: These data represent the initial European experience with the ProSeed implant method. All patients received the minimum required D90 dose (>140 Gy) and safe urethral and rectal doses. The data demonstrates that intra-operative dosimetric adjustment can assure quality control during the procedure.

577 ORAL

Bone alkaline phosphatase & extent of skeletal disease burden in a clinical trial of atrasentan are predictive of clinical disease progression in hormone refractory prostate cancer

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Purpose: Bone alkaline phosphatase (BAP) is a marker of tumor induced bone remodeling in metastatic prostate cancer. We hypothesized that baseline BAP correlates with skeletal burden of disease on bone scan in hormone refractory prostate cancer (HRPCa) and can provide prognostic information about clinical disease progression.

Methods: 288 HRPCa patients were randomized in a double blind study of atrasentan, an oral, selective ETA receptor antagonist. Patients were followed until time of clinical progression (TTP) defined as a disease-related event requiring intervention, disease-related pain requiring opiate therapy, or new lesions on imaging studies. Baseline evaluation included BAP (stratified by EORTC criteria) and the quantitative Bone Scan Index (BSI) (stratified by criteria of Sabbatini et al.).

Results: 219 patients had both baseline BAP and BSI values (median BAP 36.4 IU/L, <ULN; median BSI 1.43%). BAP and BSI values were highly correlated (r=0.80, p<0.001). Patients with low BAP (< 1.25 X ULN) had a small tumor burden, median BSI 0.51%, while patients with high BAP (~5 X ULN) had a large tumor burden, median BSI 10.5%. Both BAP and BSI correlated with TTP (see table). Median TTP was delayed by 9.6 weeks (p=0.021) in patients treated with 10 mg atrasentan. Furthermore,

increases in BAP (p<0.001) and BSI scores (p=0.08) were suppressed when compared to placebo treatment.

Bone Alkaline Phosphatase*			Bone Scan Index*		
Baseline	N	median TTP (days)	Baseline	N	median TTP (days)
< 1.25 X ULN	165	199	< 1.4%	118	202
1.25 - 5 X ULN	66	102	1.4 - 5.1%	66	169
>5 X ULN	34	78	> 5.1%	53	83

*p < 0.001, log-rank test

Conclusions: In HRPCa patients, 10 mg atrasentan delays progression as measured by clinical, biochemical, and imaging criteria. The extent of skeletal tumor burden, assessed by biochemical and bone scan measures can provide prognostic information about patients clinical disease course.

578 ORAL

Preliminary results of carbon-11 acetate pet imaging in prostate cancer patients with rising PSA after radical therapy: clinical impact to choose appropriate further treatment strategies

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Purpose: Patients after radical therapy for prostate cancer (radical prostatectomy, radiation therapy) with rising PSA continue to be a diagnostic and therapeutic challenge. Recent studies reported promising data of C-11 acetate in visualization of recurrent tumor site as well as metatastatic spread of prostate cancer. In particular, this PET tracer does not undergo urinary tract excretion and seems therefore to be suitable for evaluation of locoregional disease. This study aims to evaluate the potential role of C-11 acetate PET imaging in patients with rising PSA after radical therapy in choosing the most appropriate treatment option (local and/or systemic therapy).

Methods: 13 clinically asymptomatic patients with rising PSA and evidence of recurrent/metastatic disease by standard imaging procedures (SIP) including bone scan, CT, MRI have been evaluated. C-11 acetate dynamic imaging of the prostate region has been performed after i.v administration of 400 MBq of C-11 acetate followed by whole body scans with a PET ring scanner. In case of abnormal C-11 acetate uptake in previously unknown localizations, additional radiological work-up has been done. C-11 acetate images were analyzed by visual interpretation followed by 3D image fusion of PET with CT and/or MRI for a better anatomical localization of suspected tumor sites.

Results: In 11 out of 13 patients (85%) increased C-11 acetate uptake was found. Seven of C-11 acetate positive patients (64%) demonstrated local and/or systemic manifestations which could be confirmed by SIP. In addition, previously unknown lesions could be detected by C-11 acetate imaging in 5 of 7 patients leading to modification of the treatment strategy. The remaining 4 patients demonstrated increased C-11 acetate uptake only locally and were therefore selected as candidates for local radiotherapy with potentially curative intention. In 2 patients (PSA level 0.6 and 1.4) no tumor sites were detected in accordance to SIP.

Conclusion: Our preliminary data demonstrate the feasibility of C-11 acetate whole body PET as a promising new imaging modality to localize the tumor sites in patients with rising PSA after radical therapy. These data indicate that C-11 acetate PET scan may be helpful to select patients with local disease from those having distant metastases to choose the most appropriate therapeutic option.

Immunobiology and biological therapies

579 ORAL

Pharmacodynamic studies of the specific oral EGFR tyrosine kinase inhibitor (EGFR-TKI) zd1839 ('Iressa') in skin from cancer patients participating in phase I trials: histopathological and molecular consequences of receptor inhibition

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Aim: The specific oral EGFR-tyrosine kinase inhibitor (EGFR-TKI) ZD1839 'Iressa' is under clinical development as an anticancer agent. Since receptor inhibition by ZD1839 is required for optimal antitumour activity, we have studied in vivo the pharmacodynamic (PD) effects of ZD1839 on EGFR activation and receptor-dependent events in the skin, an EGFR-dependent tissue, in cancer patients participating in ZD1839 Phase I clinical trials.

Methods: We studied the histopathological and molecular consequences of escalating doses of daily oral ZD1839 in 104 pre- and/or on-therapy (at approximately day 28 of therapy) skin biopsies from 65 cancer patients. We measured ZD1839 effects on EGFR activation by immunohistochemistry, using an antibody specific for the activated-phosphorylated-EGFR; effects on receptor signalling (activated MAPK), proliferation, p27KIP1 and maturation were also assessed. All statistical tests were two-sided.

Results: Histopathologically, the stratum corneum of the epidermis was thinner during therapy (p<0.001). In hair follicles, prominent keratin plugs and microorganisms were found in dilated infundibula. On the molecular level, ZD1839 suppressed EGFR phosphorylation in all EGFR-expressing cells (p<0.001). In addition, ZD1839 inhibited MAPK activation (p<0.001) and reduced the keratinocyte proliferation index (p<0.001). Concomitantly, ZD1839 increased the expression of the cyclin dependent kinase inhibitor p27KIP1 (p<0.001) and of maturation markers (keratin 1 and phospho-STAT3) (p<0.001) and increased apoptosis (p<0.001). These effects on the target and EGFR-dependent molecular endpoints were observed at all dose levels, before reaching dose-limiting toxicities.

Conclusions: Oral daily ZD1839 inhibits EGFR activation and affects downstream receptor dependent processes in vivo. The observed effects may be responsible for the acneiform rashes and desquamation that are seen in some patients. Effects of receptor inhibition were profound at doses well below the one producing unacceptable toxicity, a finding that strongly supports the use of PD assessments to select optimal doses, instead of a maximum tolerated dose, for definitive efficacy and safety trials. In addition, our studies show an important role for the EGFR in normal adult skin biology and provide a rationale for the investigation of ZD1839 in EGFR-dependent skin disorders, such as psoriasis or epithelial tumours.

'Iressa' is a trade mark of the AstraZeneca group of companies.

580 ORAL

Double suicide gene therapy for locally recurrent prostate cancer

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Purpose: We have demonstrated the potential of the HSV-1 TK/GCV and E.coli CD/5-FC enzyme/prodrugs systems as cancer therapies extensively in animal model systems. The present clinical study was carried out to determine whether the intraprostatic injection of E1B-attenuated adenoviral vector containing a double suicide gene together with two prodrugs administration would be safe and exhibit any therapeutic activity in patients with locally recurrent prostate cancer following radiation therapy.

Methods: A total of twelve patients with locally recurrent prostate cancer (biopsy proven and rising serum PSA on three consecutive measurements) were entered into the trial. Three cohorts of patients were used to escalate the viral dose administration ranging from 10 to the 10vp to 10 to the 12vp. The vector used was a E1B-attenuated adenoviral vector containing HSV-1 thymidine kinase/E.coli cytosine deaminase fusion gene. Two days after the TRUS guided viral injection into the prostate, patients received a 7 day course of two prodrugs, ganciclovir and 5-fluorocytosine. Regular follow-up tests including serum PSA, prostate biopsy to determine the transgene