4 cycles. Docetaxel was given at a dose of 75 mg/m2 upon completion of each antisense infusion. Adverse reactions were assessed using the CTC criteria version 2.

Results: Ten patients were registered; 9 were treated, receiving a median of 2 cycles (range 0-4). Four pts were treated at the 5 and 7 mg/kg/day dose levels of G3139 and 1 pt received 9 mg/kg/day. Grade 4 adverse events were: 1 pt who experienced a myocardial infarction unrelated to treatment, and 5 pts who developed neutropenia. Grade 3 events possibly related to treatment were hyperglycemia (2 pts), leukopenia (4 pts), and hypophosphatemia (2 pts). Six pts are evaluable for response, 4 of whom had stable disease after 4 cycles; 2 pts progressed after 2 cycles.

Conclusions: The combination of G3139 and docetaxel is well-tolerated. The maximum tolerated dose has not yet been reached using G3139 at 9 mg/kg/day and docetaxel at 75 mg/m2. Further study of the combination is planned to better define efficacy.

802 POSTER

Association of polymorphisms at the prostate-specific antigen gene and blood circulating epithelial prostate cells

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Purpose: The prostate-specific antigen (PSA) gene is under regulation by steroid hormones. The PSA gene has a polymorphic ARE sequence with two alleles, A and G. The detection in blood of specific prostatic cells messenger RNAs has been suggested as a method of search for the presence of blood circulating prostatic cells. We hypothesize that these genetic polymorphisms at PSA gene may influence the presence of circulating prostate epithelial cells in the peripheral blood of prostate cancer patients.

Methods: In the present study we assayed PSA ARE1 genotypes and a highly sensitive reverse transcription PCR assay was used to detect the presence of mRNAs from PSA and PSM (prostate specific membrane antigen) in the blood of 61 patients.

Results: We found PSA AA genotype in 31.5% (6/19) of the PSM mRNA positive and in 52.3% (22/42) of the PSM mRNA negative cases. Regarding PSA mRNA positive cases we found that 85.6% (6/7) present the PSA AA genotype and in PSA mRNA negative cases only 38.8% (21/54) present the PSA AA genotype. This difference was statistically significant (p=0.018).

Conclusion: These results indicate that polymorphism in the PSA gene promoter influences the presence of PSA mRNA positive blood circulating epithelial cells and that may help to understand the biological mechanisms of metastization in prostate cancer.

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803 POSTER

A randomized phase II study comparing tolerance and efficacy of goserelin ('Zoladex') alone or combined with raltitrexed ('Tomudex'), in high-risk advanced prostate cancer (PCa): preliminary results on tolerance

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Introduction: So far chemotherapy has been mostly evaluated in end-stage androgen-independent PCa where it has limited efficacy. Since PCa often contain a primarily sub-population of androgen-insensitive cells, it is reasonable to expect that early application of chemotherapy will delay the onset of hormone-independence. The objective of this randomized, prospective Phase II study was to compare tolerance and efficacy or a treatment with goserelin acetate ('Zoladex') alone or combined with raltitrexed ('Tomudex') in patients with high-risk PCa.

Material & Methods: 25 patients were enrolled in the study between 01/1999 and 06/2000. Patients were aged 70 years or less with histologically confirmed PCa (Gleason score ~8 for those aged > 55 years) and had N+ or M+ disease at diagnosis. Patients with biochemical failure were included if PSA doubling time was <10 months and recurrence occur within 12 months after radical prostatectomy with or without radiotherapy. Patients received goserelin acetate (10.8 mg sc depot every 12 weeks) alone or combined with raltitrexed (3 mg/m* iv every 21 days for 6 months). Toxicity was monitored using NCI common toxicity criteria evaluation.

Results: Of the 25 patients were enrolled in this study, 18 receiving the combination regimen. A total of 85 cycles of raltitrexed were administered. Grade 1 and 2 endocrine toxicity (hot flushes) was recorded in a total of 19 patients from boths groups. In the goserelin/raltitrexed group, 19 grade 1or 2 adverse events were reported in 14 patients: grade 2 fever (in the absence of neutropenia, defined as absolute granulocyte count <1.0 x 109/L) in 12 patients; reversible grade 2 liver toxicity in 2 patients, grade 2 endocrine toxicity (hypoglycemia) in 2 diabetic patient, grade 1 neutropenia in 10 patients. Complete response as defined by a normalisation of the PSA was observed in 4 patients from the gosereline group and in 17 from the gosereline/raltitrexed group. Two patients had dose reduction for a decrease renal function

Conclusions: These preliminary results indicate that the combination of goserelin acetate and raltitrexed is safe and well tolerated in patients with high-risk PCa. Whether or not the combination results in a clinical benefit to patients will require longer follow-up. 'Tomudex' and 'Zoladex' are trade marks, the property of Zeneca Ltd (part of AstraZeneca).

804 POSTER

The efficacy of endocrine combination therapy with aminoglutethimide and hydrocortisone in metastatic prostatic cancer refractory to standard endocrine therapies

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Metastatic prostate cancer, progressive after first- or second-line anti-androgen treatment is considered hormone-resistant and remaining treatment options are limited. The adrenal gland is an important source of androgens and after conversion by aromatase indirectly of estrogens. Adrenalectomy has been used as second-line endocrine therapy. Evaluation of treatment efficacy was hampered by absence of evaluable tumour parameters. Presently, PSA is accepted as an adequate surrogate marker for response evaluation. In a prospective phase II study we investigated the combination of the aromatase inhibitor aminoglutethimide 1000 mg/day and hydrocortisone 40 mg/day in 35 patients (pts) with metastatic prostatic cancer resistant to first-or second-line endocrine therapy. Biochemical (change in PSA) and subjective response were used as main determinants for response evaluation. In addition, if evaluable lesions were present, objective assessment was done by CT scan and X-ray investigations. Main patient characteristics were median age: 67 years; median WHO performance status: 1; sites of metastases, bone: 94%, lymphnode: 17% and lung: 3%. PSA was measured every month. In 3 pts (9%) the PSA value normalised and in 10 pts (29%) a decline in serum levels of at least 50% occurred (CR + PR: 37%). Moreover, 17 pts (49%) remained stable (total benefit 86%). Median time to progression in responding and all pts were 9.5 and 5 months, respectively (range 0.5-23.5 months). Median survival for these groups was 23 and 14.5 months, respectively. Of 7 pts with measurable disease 2 showed a PR and 5 stable disease. Improvement in general condition, pain, feeling of well being was noted in two-thirds of pts. Therapy was well tolerated with only 8 adverse event episodes, mostly grade I/II and 2 cases of grade III skin toxicity. In conclusion, aminoglutethimide in combination with hydrocortisone is a valuable active and tolerable second-or third-line palliative therapy for pts with hormone-resistant prostatic cancer.

805 POSTER

Optimal brachytherapy for prostate cancer: LDR vs HDR - the view from radiobiological models, or "you take the high road and i'll take the low road"

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Purpose: Clinical evidence points to superior outcome with dose-escalation and suggests that brachytherapy may achieve superior dose-escalation when compared with external-beam for localized prostate cancer.

Methods & Materials: An algorithm based on the LQ model is constructed for fractionated and protracted irradiation. It includes tumor cell-line derived LQ parameters, repopulation, repair kinetics and isotope decay. Dose inhomogeneities for LDR (I-125 and Pd-103) and HDR (Ir-192) from patient-derived DVH are incorporated. Three risk groups are defined in terms of radiobiological parameters to correspond to clinical risk: Favorable - iPSA<10, bGS<7 and stage T2, Intermediate - one factor increased, and Unfavorable - two factors increased. Tumor control probabilities (TCP) are predicted for LDR monotherapy and for LDR and HDR boost after 45Gy EBRT. Several HDR regimens are considered.

Results: LDR brachytherapy is less susceptible to uncertainties in alpha/beta than EBRT or HDR, and more susceptible to repopulation. Model TCP for each regimen and risk group are compared with clinical series (Table 1). Dependence upon biologic assumptions will be discussed.