PSA will be achieved at higher dose levels is not known. However, the modest effect on PSA observed to date suggests some biologic activity. Once MTD is reached, phase II trials of CV787 alone and in combination are planned.

798 POSTER

Baseline quality of life measured with the EORTC QLQ-C30 helps to select a subset of 'good prognosis' metastatic hormone refractory prostate cancer patients

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Introduction and Objectives: Patients with metastatic hormone refractory prostate cancer (HRPC) are often viewed as an homogeneous group with median overall survival lasting about one year. Few prognostic factors have been identified so far. Quality of life (QL) measurements have rarely been considered as potential prognostic factors in this disease. Using data from 494 metastatic HRPC patients randomized in three EORTC trials (30903, 30921, 30944), we attempted to form three prognostic groups using clinical and biochemical parameters together with the results from baseline QL assessment.

Material and Methods: The 15 scales from the EORTC QLQ-C 30 (version 1.0) and ten baseline clinical and biochemical variables were considered. Univariate and multivariate Cox proportional hazard models stratified for trial and treatment were used. The 0.01 statistical significance level was used.

Results: Insomnia, dyspnoea and appetite loss, age, bone scan result, performance status (WHO PS) and hemoglobin level were independent predictors of survival in the multivariate analysis. Based on these 7 factors, a prognostic index was computed: PI=0 2 (if dyspnoea 67-100) 1 (if insomnia 33) 2 (if insomnia 67-100) 1 (if appetite loss 33) 2 (if appetite loss 67-100) 1 (if age 66-75) 2 (if age >75) 1 (if 5-15 hot spots) 2 (if >15/superscan) 2 (if WHO PS >1) 2 (if Hemoglobin WHO grade >0). The patients could then be classified into three groups: good prognosis (PI 0-3: 29%) with 18.7 months median survival, intermediate prognosis (PI 4-6: 39%) with 11.9 months median survival and poor prognosis (PI >6: 32%) with a median survival of 6.0 months.

Conclusion: QL dimensions of insomnia, dyspnoea and appetite loss add independent prognostic information over clinical and biochemical factors such as age, performance status, hemoglobin and bone scan results for predicting the survival of HRPC patients. They enable the definition of three groups of HRPC patients with median duration of survival from 6.0 months (poor prognosis) to 18.7 months (good prognosis). Twenty-nine percent of the patients fall in the 'good prognosis' group.

799 POSTER

Androgen suppression of advanced prostate cancer: intermittent or continuous therapy?

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Purpose: In up to 80% of advanced prostate cancer patients, the condition is improved by endocrine androgen ablative therapy. However, over time androgen independence occurs, leading to progression of the cancer. In the last few years a new therapeutic concept of hormonal treatment has emerged based on the observation that when androgen-dependent Shionogi Carcinoma in mice are intermittently exposed to androgen withdrawal, apoptotic regression of the tumour is induced. While continuous androgen suppression (CAS) can lead to a loss of libido and sexual function, intermittent androgen suppression (IAS) may improve the quality of life of patients in the intervals between hormone treatments. Data from pilot studies suggest that the cyclical effects of such treatment modality could be monitored by measuring prostate specific antigen (PSA) concentration. To obtain more data on IAS an international, prospective, randomised clinical trial was initiated in 1998. The primary objective of this study was evaluation of time to clinical tumour progression and/or PSA escape (defined as PSA concentrations over 50 ng/ml). The major secondary objective was evaluation of patients' quality of life.

Methods: Proven advanced prostate cancer patients showing normalisation of PSA (below 4 ng/ml) after 6 months of maximal androgen blockade using the combination of buserelin depot and nilutamide, became eligible for randomisation to either IAS or CAS. In total 193 patients have been randomised, 155 classified as T2-4NxM1 and 38 classified as T2-4N1-3M0. The first patient was entered in March 1998 and the follow-up of all patients enrolled ends in August 2001.

Results: Interim analyses suggest that the patients enrolled are performing well. On average, patients randomised to intermittent therapy had to restart therapy at month 14. The safety profile evaluated to date demonstrated good tolerability. At time of analysis, a total of 66 patients were withdrawn, 25 patients in the IAS group, 41 patients in the CAS group. Reasons for withdrawal were mainly clinical progression; other reasons were patient's wish or death from prostate cancer or another cause.

Conclusion: This international, prospective, randomised trial suggests that IAS is a feasible alternative to CAS.

800 POSTER

A designer inhibitor of a novel protein-kinase causes regression of human hormone refractory prostate cancer xenografts in nude mice

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A Src-related kinase, previously considered to be restricted to hemapoietic cells, was found to be expressed in the normal prostate gland. Moreover, its level is markedly elevated in prostate cancer, as determined by immmunohistochemistry and in-situ hybridization utilizing a probe specific to that kinase. The prostate gland in knockout mice for that kinase, resembled the morphology found in castrated animals. Therefore we set out to test a designer compound, directed against this kinase, for the treatment of Hormone Refractory Prostate Cancer (HRPC).

Our comparative analysis of the kinase domain revealed a distinct structural motif allegedly involved in substrate-binding. Short peptides (7 aa) derived from this region specifically inhibit substrate-phosphorylation by that kinase and abrogate the proliferation of HRPC cells (PC3 and DU-145) in-vitro at sub-micromolar range. Following structural optimization, a lead compound, KRX-123, was formulated for i.v. injection and tested for its in-vivo efficacy against established DU-145 tumors in nude mice (around 400 sq.mm at the initiation of treatment).

Once a week injection of 2.5 to 10 mg/kg of KRX-123 caused complete inhibition of tumor growth within a month, while in the control group, the tumor doubled in size during the same period of time (n=6 in each group). In the high-dose group, approximately two-third of treated animals had non-palpable remnant, by week 12. Pre-Clinical studies in rats and dogs showed that KRX-123 is non-toxic at that concentration range.

In conclusion, a promising drug candidate has been discovered for prostate cancer. A phase I/II clinical trial, testing KRX-123 in patients suffering from HRPC, is scheduled to begin in 2001.

801 POSTER

BCL-2 antisense (G3139) plus docetaxel for treatment of progressive androgen-independent prostate cancer

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Purpose: G3139 (Genta, Inc., Berkeley Heights, NJ) is an 18 mer phosphorothioate antisense oligonucleotide that targets the mRNA of BCL2, which encodes an antiapoptotic protein that is expressed in androgen-independent prostate cancer. BCL2 has also been implicated in resistence to treatment. Preclinical data have shown that G3139 has synergistic antitumor effects when used in combination with docetaxel (Taxotere®, Aventis Pharmaceuticals, Parsippany, NJ) in xenograft models. The purpose of this trial was to define the dose of G3139 with docetaxel for the treatment of patients with progressive androgen-independent prostate cancer.

Methods: Patients (pts) were treated with escalating doses of G3139 of 5, 7, and 9 mg/kg/day in cohorts of 3-6. G3139 was delivered as a five-day continuous intravenous infusion, every 3 weeks, for a maximum of