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COMBINATION THERAPY WITH AN LHRH AGONIST AND FLUTAMIDE AT VARIOUS STAGES OF PROSTATE CANCER: 7-YEAR CLINICAL EXPERIENCE

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Three hundred and sixty-three patients with clinical stage D2 prostate cancer who had not received previous endocrine therapy or chemotherapy were treated with the combination therapy using the pure antiandrogen Flutamide and the LHRH agonist [D-Trp^6, des-Gly-NH$_2$^{10}]LHRH ethylamide (or orchiectomy) for an average of 771 days (24-2607 days). Only 31 of the 308 evaluable patients (10.1%) did not show an objective positive response at the start of the combination therapy compared with an average of 18% in five recent studies using monotherapy. The median survival achieved using monotherapy is approximately 24 months while, in the present study, it is increased to 41.2 months, thus giving an additional 17 months of survival with the combination therapy. It should be mentioned that at the time of relapse, combination therapy is continued and, in addition, further blockade of adrenal androgen secretion is achieved. While our studies showing the advantages of combination therapy with pure antiandrogens have been confirmed by independent large-scale randomized studies, our preliminary data in early stage prostate cancer clearly suggest the interest of downstaging early stage prostate cancer by temporary combination therapy prior to radical prostatectomy.

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A MULTICENTRE RANDOMISED TRIAL COMPARING THE LHRH AGONIST 'ZOLADEX' WITH 'ZOLADEX' IN COMBINATION WITH FLUTAMIDE IN THE TREATMENT OF ADVANCED PROSTATE CANCER

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On behalf of the "International Prostate Cancer Study Group"

Between April 1986 and May 1987, 589 patients were recruited from ten countries into a multicentre, radomised trial comparing 'Zoladex' with a combination of 'Zoladex' and the nonsteroidal antiandrogen flutamide. 'Zoladex' was administered as a depot injection every 28 days and flutamide was given as three 250 mg tablets daily.

Patients with histologically confirmed locally advanced (T3/T4) or metastatic (M1) carcinoma were included. Previous hormone therapy, anti-hormone therapy, chemotherapy or patients having had an orchidectomy were excluded.

Sixty-five per cent of patients had metastatic disease. Both treatment groups were balanced demographically (T-category, histology, metastases, performance status). An analysis of subjective and objective response, time to response and time to progression has shown no statistically significant difference. A survival analysis after a median follow-up of 24 months has shown no statistically significant difference between the two treatment groups (p=0.47).

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ZOLADEX^R AND FLUTAMIDE VERSUS BILATERAL ORCHIECTOMY: A RANDOMIZED PHASE III TRIAL 30853 STUDY

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A total of 327 patients with metastatic prostatic cancer were randomized to either bilateral orchiectomy or treatment with Zoladex depot supplemented by Flutamide 250 mg 3 q.d. The distribution of patient and disease characteristics was well balanced in the two treatment groups except that a higher percentage of patients on orchiectomy had severe extent of disease, 80% versus 71%. Statistically significant increases in time to subjective (p = 0.02) and objective (p = 0.03) progression were recorded in favour of the combination treatment. No differences in time to death by cancer or overall death were recorded for a median duration of survival 2.5 years (p = 0.89). The clinical significance of these differences will be reassessed once additional follow-up is available and further analysis of the overall clinical material has been carried out.

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TREATMENT OF NEWLY DIAGNOSED STAGE D$_2$ PROSTATE CANCER WITH LEUPROLIDE AND FLUTAMIDE OR LEUPROLIDE ALONE, PHASE III, INTERGROUP STUDY 0036, Updated Results.

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In order to test the hypothesis of complete androgen blockade for advanced prostate cancer (D_2CaP), an intergroup trial was instituted in 1985 comparing Leuprolide (L) alone to the combination of L with Flutamide (F). Eligibility requirements included previously untreated histologically confirmed stage D_2CaP, measurable bone or soft tissue metastases, performance status (PS) of 3 or better, acceptable renal and hepatic function, no severe cardiac disease, and no prior or concomitant endocrine therapy. Stratification at entry was on the basis of PS and none or minimal disease (MD) versus severe degree (SD) of bone metastases. 617 patients were entered into this study between March 1985 and April 1986. At the present time, there is a 3-month difference in the median progression-free survival (13.9 vs 16.9 months; p = 0.039) and a 7.1-month difference in survival (27.9 vs 35.01 months; p = 0.035) favoring L + F. In L + F-treated patients with good PS + MD, the median survival recently has been reached and is 51.9 months versus 39.6 months for L + P patients. The 107 black patients in the study had median survival of 26.4 months versus 33.3 months for whites. Discussions of racial differences in survival as well as other prognostic factors will be presented. The combination of L + F is superior to treatment with L alone. The benefits appear greatest in patients with minimal disease.