SUMMARY

ZENECA PHARMACEUTICALS

FINISHED PRODUCT: CASODEX™ tablet

ACTIVE INGREDIENT: Bicalutamide (ICI 176,334)

Trial title (number): A multicentre randomised trial to compare the effect of two blinded doses of CASODEX (Zeneca 176,334; 100 mg and 150 mg orally daily) and castration in the treatment of advanced carcinoma of the prostate (176,334/0307)

Clinical phase: III

First patient recruited: 10 January 1992
Last patient recruited: 30 June 1993
Zeneca approval date: 19 January 2000

Publications: Verhelst J, Denis L, Van Vliet P, Van Poppel H, Braeckman J, Van Cangh P, et al. Endocrine profiles during administration of the new non-steroidal anti-androgen Casodex in prostate cancer. Clin Endocrinol 1994;41(4)525-530.

Tyrrell CJ. Tolerability and quality of life aspects with the anti-androgen CASODEX (ICI 176,334) as monotherapy for prostate cancer. Eur Urol 1994;26 (Suppl 1):15-19.

Tyrrell C. A randomised comparison of CASODEX 150 mg versus castration in the treatment of advanced prostate cancer. Proc Am Soc Clin Oncol 1996;15:192 (Abstract 411).

Tammela T. A randomised comparison of CASODEX 150 mg versus castration in the treatment of advanced prostate cancer. Cancer Eur Urol 1996; 30 Suppl 2: 265 (Abstract 993).

Chamberlain M. A randomised comparison of CASODEX 150 mg versus castration in the treatment of advanced prostate cancer. Aust NZ J Surg 1997; 67(6):368.

Iverson P. A randomised comparison of CASODEX 150 mg versus castration in the treatment of advanced prostate cancer. Brit J Urol 1997; 80 (Suppl 2):279 (Abstract 1098).

Anderson J. Improvements in quality of life for patients treated with a non-steroidal antiandrogen ‘CASODEX’ (Bicalutamide) 150 mg as monotherapy compared to castration. Eur Urol 1998; 33 (Suppl 1):87 (Abstract 348).

Iverson P. A randomised comparison of Bicalutamide ('CASODEX') 150 mg versus castration in the treatment of advanced prostate cancer. Eur Urol 1998;33 (Suppl 1):87 (Abstract 347).

Iverson P. Prospects for improving survival in early prostate cancer: Results and ongoing studies with the non-steroidal antiandrogen Bicalutamide (CASODEX). J Urol 1998;159(5) (Suppl):338 (Abstract 1301).

Tyrrell C. Improvements in subjective response in patients with advanced prostate cancer treated with 'CASODEX' (Bicalutamide) 150 mg monotherapy compared with castration. Proc Am Soc Clin Oncol 1998;17:315a (Abstract 1214).

Iverson P. CASODEX (Bicalutamide) 150 mg monotherapy compared with castration in patients with previously untreated non-metastatic prostate cancer: Results from two multicentre randomised trials at a median follow-up of 4 years. Urology 1998;51(3):389-396.

Tyrrell C. A randomised comparison of 'CASODEX' (Bicalutamide) 150 mg monotherapy versus castration in the treatment of metastatic and locally advanced prostate cancer. Eur Urol 1998;33(5):447-456.

Kaisary AV. Exploratory post-hoc survival evaluation in M1 prostate cancer patients treated with Bicalutamide ('CASODEX'). Ann Oncol 1998;9 (Suppl 4):57 (Abstract 2730).

OBJECTIVES

The objectives of this trial were to compare in conjunction with Trial 176,334/0306: CASODEX 100 mg and 150 mg daily in terms of tolerability, and efficacy; and the selected dose of CASODEX with medical or surgical castration in terms of efficacy, tolerability, and quality of life (QoL) in patients with previously untreated advanced prostate cancer.

The objectives were revised as a result of the analysis in March 1995. The revised objectives were to compare the selected dose of CASODEX (150 mg once daily) with medical or surgical castration in terms of survival, time to progression, time to treatment failure, QoL, and tolerability in patients with previously untreated locally advanced prostate cancer.

METHODS

Design:

Randomised, 2-stage, multicentre trial conducted in Europe, Australia, and South Africa. Stage I compared 2 blinded doses of CASODEX with castration on a 2:2:1 randomisation basis. Patients randomised to castration could choose treatment either by medical (ZOLADEX™) or surgical (bilateral orchidectomy) methods. The dose-selection decision was made on the basis of fall in prostate-specific antigen (PSA) levels at a minimum of 12 weeks of follow-up and safety data in a combined analysis of 135 patients in this trial and 18 patients in Trial 176,334/0306, a Phase III trial conducted in Scandinavia with an identical design to the current trial. Stage II compared the chosen CASODEX dose (150 mg daily) with castration.

Population:

Nine hundred and eighty-five patients with previously untreated prostate cancer.

Key inclusion criteria:
Histologically or cytologically diagnosed prostate cancer, either metastatic or locally advanced, with PSA levels at least 5 times the upper limit of the reference range; evaluable disease; fit for orchidectomy.

Key exclusion criteria:
Previous or concurrent systemic therapy for prostate cancer, including orchidectomy, anti-androgens, oestrogens, luteinising hormone-releasing hormone analogues, ketoconazole or cytotoxic therapy; previous radiotherapy to the prostate within the 3 months preceding entry into the trial; previous history within the past 5 years, or presence, of an invasive malignancy other than prostate cancer or squamous/basal cell carcinoma of the skin; an Eastern Co-operative Oncology Group (ECOG) performance score of 3 or 4; a serum bilirubin value of ≥1.26 times the upper limit of the reference range.

Dosage:
In Stage I, patients were randomised in a 2:2:1 ratio to 1 of 3 treatment groups: CASODEX 100 mg, CASODEX 150 mg, or castration. In Stage II, patients were randomised in a 2:1 ratio either to receive CASODEX 150 mg or to undergo castration. In order to blind the trial with respect to the dose of CASODEX administered, each patient randomised to CASODEX received 3 tablets once a day: 3 CASODEX 50 mg tablets in the CASODEX 150 mg group, and 2 CASODEX 50 mg tablets plus a matching placebo tablet in the CASODEX 100 mg group. All tablets were taken orally. Patients randomised to castration could choose between undergoing bilateral orchidectomy or receiving ZOLADEX™ 3.6 mg subcutaneous depot injections every 28 days.

Key assessments:
The primary endpoints were:

- survival (the number of days between randomisation and death)
- time to treatment failure (the number of days between randomisation and treatment failure)

The secondary endpoints were:

- QoL including subjective response derived from ECOG activity scores, cancer-related pain scores, and cancer-related analgesic requirement scores recorded at intervals throughout the trial
- time to progression
- safety

Biochemistry variables and PSA levels were assayed at intervals throughout the trial. All adverse events were recorded and followed up until resolution.

Statistical Methods:
Cox's proportional hazards model was used to analyse the time to death, treatment failure, and progression. The fitted models allowed for the effects of randomised treatment, testosterone, and PSA concentrations at entry, ECOG performance score at entry and race. Quality of life was analysed using analysis of covariance (ANCOVA). The models fitted were to include terms for treatment, centre, centre-by-treatment interaction, and dimension score at entry.

RESULTS

Efficacy and safety data were first analysed after approximately 40 weeks of follow-up in September 1993. Following a review by an independent Data Monitoring and Safety Committee (DMSC), the data were considered too immature for any reasonable conclusions to be drawn as only 9% of patients (in Trials 0306 and 0307 combined) had died. A second analysis, based on a 31 December 1994 data cut-off, showed a qualitative interaction with respect to survival outcome in the combined analysis of the two trials between metastatic status at baseline and randomised treatment and because of this M0 and M1 data were analysed separately. The combined data for M1 patients were considered mature (43% of patients having died) and, on the advice of the DMSC, all M1 patients were withdrawn from the trials and offered standard therapy for advanced disease. The DMSC further recommended that M0 patients continued receiving randomised treatment with a further analysis to be conducted when the combined data were of greater maturity. A subsequent analysis was therefore carried out after approximately a median of 200 weeks of follow-up (data cut-off date 31 December 1996) at which time the combined mortality was 31%. The DMSC reviewed the data and recommended a further follow-up assessment after approximately another 12 months of treatment. This analysis was performed in May 1998 (based on a data cut-off date of 1 March 1998) at which time the median follow-up was 5 years and the combined mortality was 42%. This analysis was performed primarily in response to requests from European regulatory authorities who were, at that time, reviewing the earlier 31% analysis. A review of these results continued to reveal no safety issues, and the DMSC recommended further follow-up until >50% of patients had died. In August 1999 based on a data cut-off of 1 June 1999 the DMSC reviewed the most recent combined M0 data after a median of 6.3 years follow-up (which showed a combined mortality of 56%), and saw no overall difference in survival and concluded that the data were mature. The current report provides the results of an updated efficacy and safety analyses for M0 patients based on a data cut-off date of 1 June 1999.

Demography:

A total of 985 male patients was randomised into this trial. Of these, 407 had M0 disease (234 CASODEX 150 mg; 118 castration; 55 CASODEX 100 mg) and 578 had M1 disease (342 CASODEX 150 mg; 165 castration; 71 CASODEX 100 mg). The treatment groups were well balanced in terms of age, weight, and race for both M0 and M1 patients. The baseline cancer status also appeared to be well balanced across the treatment groups with the majority of patients in each treatment group having a tumour stage category of T3 and an ECOG performance score of 0 (full activity). Median plasma PSA levels at baseline were slightly higher for patients receiving CASODEX 150 mg (101.0 ng/ml all patients, 66.4 ng/ml M0 patients, 171.3 ng/ml M1 patients) compared with castration (91.5 ng/ml, 61.7 ng/ml, and 145.1 ng/ml, respectively) but only small differences were observed in plasma testosterone levels.

Time to event endpoints - M0 patients:

The results of the analysis of ‘time to event’ data comparing treatment with CASODEX 150 mg and castration are presented in Table I. Estimated median time to event are presented in Table II.

Table I Analysis of time to event data: M0 patients

Endpoint	CASODEX 150 mg: castration			
	Hazard ratio	Upper 1-sided 95% confidence limit	2-sided 95% confidence interval	p-value
Time to death	1.253	1.627	0.917 to 1.711	0.1571
Time to treatment failure	1.250	1.527	0.985 to 1.587	0.0659
Time to disease progression	1.408	1.762	1.078 to 1.839	0.0122

Table II Estimated median time to event: M0 patients

Event	Number of patients assessed	Number (%) of events		Estimated median time to event (days)[a]
Death				
CASODEX 150 mg	234	136	(58.1)	1840
Castration	118	57	(48.3)	2203
Total	352	193	(54.8)	NC
Treatment failure				
CASODEX 150 mg	234	218	(93.2)	678
Castration	118	103	(87.3)	812
Total	352	321	(91.2)	NC
Disease Progression				
CASODEX 150 mg	234	187	(79.9)	922
Castration	118	79	(66.9)	1085
Total	352	266	(75.6)	NC

[a] Kaplan-Meier estimate.
NC Not calculated.

These data show there was no statistically significant difference between the treatment groups in terms of the primary endpoints of survival and time to treatment failure, although it was not possible to conclude equivalence as the upper 1-sided 95% confidence limit was greater than 1.25. The estimated absolute differences were in favour of castration although the differences were not statistically significant. There was a statistically significant difference in favour of castration for time to disease progression.

Secondary efficacy endpoints - M0 patients:

There were no statistically significant differences between the treatment groups with respect to the QoL dimensions analysed at 12 months but there was evidence of improved physical capacity for patients receiving CASODEX 150 mg (p=0.0867).

There were no apparent differences in objective assessments between the treatment groups. Subjective response was not analysed as there were insufficient data to perform such an analysis.

Time to event endpoints - M1 patients:

The results of the analysis of ‘time to event’ data are presented in Table III.

Table III Analysis of time to event data - M1 patient

Endpoint	CASODEX : castration			
	Hazard ratio	Upper 1-sided 95% confidence limit	2-sided 95% confidence interval	p-value
Time to death	1.312	1.688	0.971 to 1.772	0.0767
Time to treatment failure	1.489	1.799	1.189 to 1.865	0.0005
Time to disease progression	1.494	1.823	1.179 to 1.894	0.0009

For patients with M1 disease there was no statistically significant difference in time to death between the groups, but it was not possible to conclude equivalence. Time to progression and treatment failure were statistically significant in favour of castration.

Secondary efficacy endpoints - M1 patients:

A statistically significant difference (p=0.0131) in favour of CASODEX 150 mg was observed for the sexual interest QoL dimension. There were no apparent differences in objective assessments between the treatment groups. There were no significant differences between the treatment groups in the subjective assessments performed on these patients.

Safety: A total of 570 patients (M0 and M1) received CASODEX 150 mg for a mean duration of 117.54 weeks, and a total of 282 castrated patients were exposed for a mean duration of 145.82 weeks.[1] A total of 94 (16.5%) M0 or M1 patients withdrew from treatment with CASODEX 150 mg as a result of adverse events compared with 38 (13.6%) patients in the castration group. Adverse events in the entire trial population were generally well balanced between the treatment groups with the exception of expected pharmacological effects of gymaecomastia and male breast pain with CASODEX treatment and hot flushes with castration.

The primary causes of death were similar in both treatment groups, but cardiovascular events led to more deaths in the castration group than in the CASODEX 150 mg group.

No major differences between the treatment groups were observed in the adverse events leading to withdrawal, serious adverse events or laboratory parameters.

[1] Patients who received orchidectomy as their castration treatment were not able to stop therapy. The calculated exposure times for this group of patients takes into account the time that patients who had undergone orchidectomy remained in the trial.