SUMMARY

ZENECA PHARMACEUTICALS

FINISHED PRODUCT: CASODEX™ tablet

ACTIVE INGREDIENT: Bicalutamide (ICI 176,334)

Trial title (number): A multicentre randomised study 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 (176,334/0306)

Clinical phase: III

First patient recruited: 13 May 1992
Last patient recruited: 30 June 1993
Zeneca approval date: 14 January 2000

Publications: 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;0 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;7(6):368.
Iverson P. A randomised comparison of CASODEX 150 mg versus castration in the treatment of advanced prostate cancer. Brit J Urol 1997;0 (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;3 (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;3 (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;59(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;7:315a (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;1(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;3(5):447-456.
Kaisary AV. Exploratory post-hoc survival evaluation in M1 prostate cancer patients treated with Bicalutamide ('CASODEX'). Ann Oncol 1998; (Suppl 4):57 (Abstract 2730).

OBJECTIVES

The objectives of this trial were to compare in conjunction with Trial 176,334/0307: CASODEX 100 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 Scandinavia. 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 12 weeks minimum follow-up and safety data in a combined analysis of 18 patients in this trial and 135 patients in Trial 176,334/0307, a Phase III trial conducted in Europe, Australia, and South Africa with an identical design to the current trial. Stage II compared the chosen CASODEX dose (150 mg daily) with castration.

Population: Four hundred and sixty-eight men 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 receive CASODEX received 3 tablets orally 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 Eastern Co-operative Oncology Group 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 468 patients was randomised into this trial. Of these 140 had non-metastatic (M0) disease (86 CASODEX 150 mg; 42 castration; 12 CASODEX 100 mg) and 328 had metastatic (M1) disease (202 CASODEX 150 mg; 99 castration; 27 CASODEX 100 mg). The demographic data appeared well balanced across the treatment groups. At the data cut-off date, 1 June 1999, 58 (69.9%) M0 patients in the CASODEX 150 mg arm and 32 (74.4%) M0 patients in the castration arm had been withdrawn.

Time to event endpoints - M0 patients:

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

Table I Analysis of time to event data: M0 patients

	CASODEX 150 mg: castration			
Endpoint	Hazard ratio	Upper 1-sided 95% confidence limit	2-sided 95% confidence interval	p-value
Time to death	0.637	0.955	0.394 to 1.031	0.0667
Time to treatment failure	0.700	0.984	0.467 to 1.050	0.0848
Time to disease progression	0.751	1.068	0.494 to 1.143	0.1813

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	86	46	(53.5)	2064
Castration	42	28	(66.7)	1799
Total	128	74	(57.8)	NC
Treatment failure				
CASODEX 150 mg	86	70	(81.4)	1203
Castration	42	37	(88.1)	609
Total	128	107	(83.6)	NC
Disease progression				
CASODEX 150 mg	86	68	(79.1)	1414
Castration	42	34	(81.0)	836
Total	128	102	(79.7)	NC

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

Time to treatment failure data were most mature with a total of 107 (83.6%) events, with time to progression having 102 (79.7%) events and time to death having 74 (57.8%) events.
For each of these endpoints, there was no statistically significant difference between the groups at the conventional 5% statistical significance level. In each case, the estimated difference was in favour of CASODEX 150 mg. From the hazard ratio data, the risk of an event on CASODEX 150 mg was 36%, 30%, and 25% lower than that on castration for time to death, treatment failure, and progression, respectively. The upper 1-sided confidence limit was less than 1.25 for each of these endpoints, indicating that CASODEX 150 mg was at least as effective as castration.

Secondary efficacy endpoints - M0 patients:

There was a statistically significant benefit ($p = 0.0174$) in favour of CASODEX 150 mg in terms of the sexual interest quality of life dimension at 12 months. None of the other dimensions showed a statistically significant difference between the treatment groups. 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 analyses of ‘time to event’ data are presented in Table III.

Table III Analysis of time to event data - M1 patients

Endpoint	CASODEX 150 mg: castration			
	Hazard ratio	Upper 1-sided 95% confidence limit	2-sided 95% confidence interval	p-value
Time to death	1.251	1.702	0.867 to 1.805	0.2319
Time to treatment failure	1.352	1.722	1.014 to 1.803	0.0398
Time to disease progression	1.347	1.729	1.001 to 1.813	0.0493

Time to treatment failure data were most mature with a total of 226 (75.1%) events, with time to progression having 214 (71.1%) events and time to death having 139 (46.2%) events.
There was no statistically significant difference between the groups in terms of survival but it was not possible to conclude equivalence as the upper 1-sided 95% confidence limit exceeded 1.25. There was a statistically significant difference in favour of castration for disease progression (p=0.0493) and time to treatment failure (p=0.0398). From the hazard ratio data, the risk of an event on CASODEX 150 mg was 35%, 35%, and 25% higher than that on castration for time to treatment failure, progression, and death, respectively.

Secondary efficacy endpoints - M1 patients:

For the quality of life dimensions, there was no statistically significant difference between the groups, although there was a trend towards a reduction in pain in the CASODEX 150 mg group (p=0.0570). The odds of a subjective response were 2.4 times greater for a patient randomised to the CASODEX 150 mg group than for a patient randomised to the castration group. This suggests a benefit for CASODEX 150 mg over castration.

Safety: The most commonly reported adverse events were those which could be predicted from the pharmacological actions of the agents; gynaecomastia and breast pain were most commonly reported with CASODEX therapy, and hot flushes and sweating castration therapy. The most common non-prostate cancer related deaths were due to cardiovascular causes, as would be expected in an elderly population. Cardiovascular related deaths appeared to be more common in the castration patients than in the CASODEX patients. Despite the high incidence of pharmacologically related adverse events, there were no withdrawals due to these. Overall, the withdrawal rate was low for both treatments with no clinically significant differences evident between the groups or between M0 and M1 patients