AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: CASODEX
ACTIVE INGREDIENT: Bikalutamid

Study No: 7054TR/01
An Open Randomised Trial to Compare the Value of Prophylactic versus Therapeutic Breast Radiotherapy in CASODEX™ Monotherapy Induced Gynecomastia and/or Breast Pain in Prostate Cancer Patients. (COMART)

Developmental phase: Phase IV
Study Completion Date: 10 October 2005
Date of Report: 23 May 2008

Study centre(s)

Study was conducted in Hacettepe University, Department of Urology, Ankara, TURKEY. First patient was enrolled in June 2003.

Publications

<<None at the time of writing this report.>>

Objectives

The primary objective of this trial is:
To examine the value of prophylactic versus therapeutic breast radiotherapy in reducing the incidence of Casodex monotherapy induced gynaecomastia and/or breast pain.
Secondary objectives are:
To examine the tolerability of radiotherapy to male breast.
To examine the tolerability of Casodex 150 mg in localized and locally advanced prostate cancer patients.
To examine the efficacy of Casodex 150 mg. in prostate cancer patients.
In addition, clinical monitoring has been performed to ensure the safety of all patients while receiving CASODEX.

Study design

An open randomized multi-centre trial was conducted at 43 centers in Turkey between June 2003 and October 2005 in accordance with the Declaration of Helsinki with approvals of the Local Ethics Committees (LEC) and Central Ethics Committee. Randomized patients received either radiotherapy or no radiotherapy prior to commencing bicalutamide 150 mg monotherapy for PRT arm. Treatment with

bicalutamide 150 mg was planned to be continued for TRT arm. Scheduled assessments were performed at 3-monthly intervals for 12-months for PRT arm and at least 6 months after therapeutic breast irradiation in TRT arm.

Target healthy volunteer population and sample size

Male patients (aged ≥18 years) with localized prostate cancer (T1b–T4, any regional N, M0) and without current gynecomastia or breast pain, who have received radical prostatectomy or radiotherapy without prior hormonal therapy, with at least 1-year life expectancy were enrolled into the trial.
The sample sizes were determined to be n=120 in total at minimum (n1=70 for those who will use Casodex only at the beginning; n2=50 for patients who are given Casodex and radiotherapy) including possible drop-outs. 125 patients from 43 centers were randomized. 53 out of 125 patients were in prophylactic radiotherapy (PRT) or Casodex and radiotherapy group.
The expectation was that 80 % of the patients, receiving Casodex 150 mg. without prophylactic radiotherapy would develop gynecomastia and/or breast pain, only 20% of those receiving prophylactic radiotherapy would. Patients who didn't receive prophylactic radiotherapy (treated with Casodex only) and experience gynecomastia and/or breast pain was given radiotherapy as a treatment. It was assumed in the half of them (50%) gynecomastia and/or breast pain would regress. The sample sizes were determined to be n=101 in total at minimum (n1=56 for those who would use Casodex only at the beginning; n2=45 for patients who were given Casodex and radiotherapy) without drop-outs, in line with the values given as α= 0,05 (type I error), β = 0,10 (type II error), and Power = 0,90.

Investigational product and comparator(s): dosage, mode of administration and batch numbers'

Name of investigational product is CASODEX (Bicalutamid). CASODEX was administered in tablet form as a once daily oral dose of one 150mg tablet. Formulation number is 11156. Batch numbers are BV 111, BR 849 and BA 005.

Duration of treatment

CASODEX monotherapy was administered orally 150 mg once-daily basis and lasted for 12 months. Scheduled assessments were performed at three-month intervals in PRT arm and at least six months after therapeutic breast irradiation in TRT arm. Treatment discontinuation was observed and patients who violated protocol or did not regularly attend follow up visits were excluded from the final analysis.

Criteria for evaluation - efficacy (main variables)

The main variable was prophylactic radiotherapy (PRT) versus therapeutic radiotherapy (TRT) in CASODEX monotherapy induced gynecomastia and/or breast pain. The tolerability of radiotherapy to male breast was evaluated with the change in intensity of gynecomastia and breast pain following radiotherapy treatment. Tolerability of radiotherapy was elicited by direct questioning.

Criteria for evaluation - safety (main variables)

Safety was evaluated according to the adverse events. CASODEX may cause may cause hot flashes, constipation, general body aches, increased urination, cough, breathing trouble, swelling of the hands or feet, bloody urine, depression, flu-like symptoms (fever,

chills), unusual weakness swelling or tenderness of the breasts and liver function problems. These side effects were observed to evaluate safety.

Statistical methods

For the primary endpoint of the incidence of gynecomastia the data was analysed using proportions and the normal distribution to test the difference. The normal approximation to the binomial being suitable when n>= 50. The odds ratio and associated 95% confidence interval was also constructed to aid interpretation of the data. The treatment effect and associated 95% CI was presented.
The secondary endpoints relating to breast pain was analysed in the same manner as the primary endpoints, however there was less emphasis on formal statistical hypothesis testing as the trials were not powered on these criteria. Data collected by calliper measurements for the secondary endpoint of degree (or size) of gynecomastia was tabulated and listed.
The $\chi 2$ test, Mann Whitney U, Wilcoxon and Fisher's exact tests were used to compare groups. $P \leq 0.05$ was assigned as statistical significance level. Bonferroni correction was applied to all pair-wise comparisons.

Subject population

One hundred and thirty three patients were included to the trial. Eight patients who did not fulfill the inclusion criteria were not randomized. 125 patients from 43 centers were randomized. 53 out of 125 patients were in prophylactic radiotherapy (PRT) group and 72 patients were in therapeutic radiotherapy (TRT). One of the patients in the PRT group discontinued because of a serious adverse event which led to function loss and 124 patients were able to be analysed.
There was no significant difference between groups (PRT and TRT) in all demographic and baseline variables. Therefore treatment groups were balanced in terms of demography and baseline characteristics.

Summary of efficacy results

Prophylactic breast irradiation significantly reduced the incidence of bicalutamide induced gynecomastia in patients at one year of follow up, compared with no PRT. More patients had gynecomastia in TRT group both at the third and at the sixth months following radiotherapy. The cumulative incidence of gynecomastia in PRT and TRT groups were 13% and 75% at 3 months, and 19.6% and 87.8% at 6 months, respectively. In TRT group, breast pain ($p<0.05$) and breast tenderness ($p<0.001$) were increased significantly following RT at month 6 Table 1.

Table 1: Details of gynecomastia and breast pain between prophylactic radiotherapy and therapeutic radiotherapy arms at third and sixth month evaluation following irradiation.

	3 month (after RT)		6 month (after RT)	
	PRT, n (%)	TRT, n (%)	PRT, n (%)	TRT, n (%)
Gynecomastia (physician evaluation)				
No	40 (87.0)	10 (25)	37 (80.4)	5 (12.2)
Yes	6 (13)	30 (75)	9 (19.6)	36 (87.8)
P	<0.001		<0.001	
Breast pain (severity)				
None	27 (58.7)	14 (36.8)	22 (47.8)	9 (23.1)

	3 month (after RT)		6 month (after RT)	
	PRT, n (%)	TRT, n (%)	PRT, n (%)	TRT, n (%)
A little severe	14 (30.4)	18 (47.4)	18 (39.1)	20 (51.3)
Quite a bit severe	4 (8.7)	4 (10.5)	6 (13.0)	6 (15.4)
Much severe	1 (2.2)	1 (2.6)	0 (0.0)	3 (7.7)
Very much severe	0 (0.0)	1 (2.6)	0 (0.0)	1 (2.6)
P	0.076		0.008	
Breast tenderness (frequency)				
None or seldom	31 (67.4)	19 (50.0)	35 (76.1)	17 (43.6)
Once a week	4 (8.7)	8 (21.1)	3 (6.5)	3 (7.7)
More than once a week	7 (15.2)	4 (10.5)	6 (13.0)	10 (25.6)
Once a day	1 (2.2)	2 (5.3)	1 (2.2)	5 (12.8)
More than once a day	3 (6.5)	5 (13.2)	1 (2.2)	4 (10.3)
P	0.179		0.001	

Breast enlargements were significantly increased in TRT group compared to PRT group both in 3 ($p<0.05$) and 6 months ($p<0.001$) after RT. Patients without breast enlargement accounted for 63.6% in PRT and 25% in TRT ($p>0.05$) at month 3 after RT, whereas the values of the same groups changed to 41.7% and 28.1% ($p>0.05$) at month 6. Fewer patients felt distressed by breast pain and tenderness at 3rd and 6th months following prophylactic RT among patients.

Summary of safety results

132 adverse events, whether causally related with radiotherapy or chemotherapy were observed. However 6 out of 132 adverse events were related to Casodex in PRT group and 8 of them were related to Casodex in TRT group. Adverse events related to hormonal and radiation treatments in both arms are detailed (Table 2). Treatments were generally well tolerated with mild and moderate side effects.

Table 2: Adverse events causally related to CASODEX

Adverse event	**PRT+bicalutamide 150mg(n=53)**	**TRT+bicalutamide 150mg(n=72)**
Erythema	2	4
Hyperpigmentation	1	2
Pruritus (breast)	1	-
Hair loss	-	1
Liver function test abnormalities	2	1
Total	6	8

Conclusion(s)

A clear beneficial effect has been observed of prophylactic breast RT for the prevention of gynecomastia, breast pain and tenderness in patients treated with bicalutamide therapy in comparison to therapeutic approach following occurrence of gynecomastia in our multi

centric cohort; even though the distressing effect of breast enlargement, pain and tenderness were not statistically significant between groups. It is believed that prophylactic breast irradiation is an efficient and well tolerated approach in this context.