AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Fulvestrant
Study Code	D6997L00002 (9238SW/0001)
Edition Number	Final
Date	29 January 2010

FACT: ANASTROZOLE MONOTHERAPY VERSUS MAXIMAL OESTROGEN BLOCKADE WITH ANASTROZOLE AND FULVESTRANT COMBINATION THERAPY: AN OPEN RANDOMISED, COMPARATIVE, PHASE-III MULTICENTRE STUDY IN POSTMENOPAUSAL WOMEN WITH HORMONE RECEPTOR POSITIVE BREAST CANCER IN FIRST RELAPSE AFTER PRIMARY TREATMENT OF LOCALISED TUMOUR

Study dates: First patient enrolled: 16 January 2004
Last patient randomised: 19 March 2008
Data cut-off for primary analysis: 30 April 2009

Phase of development: Therapeutic confirmatory (III)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

Study centres

This study was conducted at 77 centres in Sweden (22 centres), Germany (17 centres), Italy (8 centres), Norway (6 centres), Turkey (6 centres), France (4 centres), Portugal (4 centres), Canada (4 centres), Costa Rica (2 centres), Finland (2 centres), and Guatemala (2 centres). The first patient was enrolled on 16 January 2004.

Publications

None at the time of writing this report.

Objectives and variables

Table S1 Study objectives and variables

Objective	Variable
Primary	
To estimate TTP at first recurrence in postmenopausal women with hormone receptor positive breast cancer treated with anastrozole monotherapy vs. patients treated with fulvestrant and anastrozole combination therapy	TTP
Secondary	
To evaluate the activity of anastrozole alone vs. the combination of fulvestrant and anastrozole by estimating the ORR	ORR (CR + PR) based on RECIST response criteria
To evaluate TTF	TTF
To evaluate DoR	DoR
To evaluate clinical benefit	CBR (CR + PR + SD ≥24 weeks) and DoCB[a]
To compare the safety and tolerability of anastrozole monotherapy vs. fulvestrant and anastrozole combination therapy	Nature, incidence and severity of AEs and SAEs; incidence of and reasons for study drug dose interruptions[b] and withdrawals; study drug exposure, laboratory assessments, physical examinations
To assess OS using the data obtained at the primary data cut-off[c]	OS (measured as median survival in each group on an ITT basis)
Exploratory	
To evaluate cause specific mortality using the data obtained at the primary data cut-off[c]	Incidence and specific cause of death in all patients who died

a Specified in the SAP.
b Dosing information was listed but not summarised; the reasons for dose interruptions were not captured.
c The prespecified analyses of OS and the assessment of cause specific mortality (defined in the SAP) were planned for when ~60% of patients had died. However, when the study outcome results became available, the decision was taken to analyse OS and assess cause specific mortality at the data cut-off for the primary analysis (when ~40% of patients had died).

AE Adverse event; CBR Clinical benefit rate; CR Complete response; DoCB Duration of clinical benefit; DoR Duration of response; ITT Intention to treat; ORR Objective response rate; OS Overall survival; PR Partial response; RECIST Response Evaluation Criteria in Solid Tumours ; SAE Serious adverse event; SAP Statistical Analysis Plan; SD Stable disease; TTF Time to treatment failure; TTP Time to progression.

Study design

This was an open-label, randomised, comparative, multi-centre, Phase-III study to evaluate TTP after treatment with fulvestrant in combination with anastrozole compared with anastrozole as monotherapy.

Target patient population and sample size

Postmenopausal women with hormone receptor positive breast cancer in first relapse after primary treatment of a localised tumour were eligible to participate; patients could have had measurable or non-measurable disease.

The sample size calculation was based on the primary variable (TTP). Median TTP in the anastrozole arm was expected to be 9 months (based on data from Studies 1033IL/0027 and 1033IL/0030). A hazard ratio of 0.75 was considered clinically meaningful; thus, median TTP in the fulvestrant + anastrozole arm was estimated to be 12 months. Approximately 380 progression events were required to have ≥80% power to detect a difference between the treatment arms using a two-sided significance level of 0.05; it was estimated that 256 patients per arm would need to be recruited to obtain this number of events.

Investigational product/comparator: dosage, mode of administration and batch numbers

Patients were randomised (1:1) to one of two treatment arms:

- Fulvestrant + anastrozole arm: fulvestrant intramuscular injection according to a loading dose regimen (an initial dose of fulvestrant 500 mg on Day 0, followed by fulvestrant 250 mg on Days 14 and 28, and every 28 [± 3] days thereafter; fulvestrant 250 mg +LD) in combination with anastrozole 1 mg orally once daily

- Anastrozole arm: anastrozole 1 mg orally once daily

Batch numbers: fulvestrant 92179B02, 22588J04, and 22589G04; anastrozole 93033A02.

Duration of treatment

Study therapy was to be continued until evidence of objective progression or undue toxicity.

Statistical methods

The hypotheses relating to treatment differences in terms of TTP, ORR, CBR, DoR, DoCB, TTF and OS were: H_0, fulvestrant + anastrozole was not different from anastrozole; H_1, fulvestrant + anastrozole was different from anastrozole. The primary analysis for TTP was a log-rank test; the secondary analysis was a Cox proportional hazards regression model with treatment factor and baseline prognostic covariates (visceral involvement, categorical age at baseline, response to last endocrine therapy, recurrence status). Supportive sub-group analyses were also performed (sub-groups were the same as the baseline prognostic covariates). A nominal significance level of 0.05 was used. The primary data cut-off was 30 April 2009.

Patient population

In total, 514 patients were randomised (fulvestrant + anastrozole arm n=258; anastrozole arm n=256; full analysis set), 510 patients received treatment (fulvestrant + anastrozole arm n=256; anastrozole arm n=254; safety analysis set), and 175 completed the study (fulvestrant + anastrozole arm n=91; anastrozole arm n=84). The treatment arms were generally well balanced with regards to demographic and baseline characteristics (Table S2).

Table S2 Demographic and key baseline characteristics: full analysis set

	Fulvestrant + anastrozole arm (n=258)	Anastrozole arm (n=256)
Demographic characteristic		
Female sex, n (%)	258 (100.0)	256 (100.0)
Age (years), mean (sd)	65.2 (9.6)	63.4 (10.3)
Age group, n (%)		
≥18 to <65 years	124 (48.1)	145 (56.6)
≥65 to <75 years	89 (34.5)	73 (28.5)
≥75 years	45 (17.4)	38 (14.8)
Race, n (%)		
Caucasian	242 (93.8)	237 (92.6)
Black	1 (0.4)	2 (0.8)
Oriental	4 (1.6)	2 (0.8)
Other	11 (4.3)	15 (5.9)
Baseline characteristic, n (%)		
Hormone receptor status		
ER+ve and PgR+ve	193 (74.8)	195 (76.2)
ER+ve and PgR-ve	60 (23.3)	51 (19.9)
ER+ve and PgR unknown	4 (1.6)	6 (2.3)
ER-ve and PgR+ve	1 (0.4)	4 (1.6)
ER-ve and PgR-ve	0 (0)	0 (0)
ER-ve and PgR unknown	0 (0)	0 (0)
Breast cancer history		
Measurable disease: yes/no	129/129 (50.0/ 50.0)	113/143 (44.1/55.9)
Recurrence[a]: local/metastatic	53/245 (20.5/95.0)	39/242 (15.2/94.5)
Disease sites at baseline		
Breast only	1 (0.4)	1 (0.4)
Bone only	63 (24.4)	71 (27.7)
Any visceral disease[b]	134 (51.9)	124 (48.4)
Previous treatment[a]		
Adjuvant endocrine therapy	180 (69.8)	168 (65.6)
No previous adjuvant endocrine therapy	78 (30.2)	88 (34.4)
Adjuvant radiotherapy	159 (61.6)	171 (66.8)
Adjuvant chemotherapy	108 (41.9)	127 (49.6)
Other previous cancer therapy	3 (1.2)	1 (0.4)
No previous cancer therapy	33 (12.8)	33 (12.9)
GnRH agonist at baseline	4 (1.6)	5 (2.0)

a Categories are not mutually exclusive.
b Patients with disease site at baseline of adrenal, abdominal, CNS, liver, lung, peritoneum, pleura, or brain.
GnRH Gonadotropin releasing hormone; ER Oestrogen receptor; PgR Progesterone receptor.

Summary of efficacy results

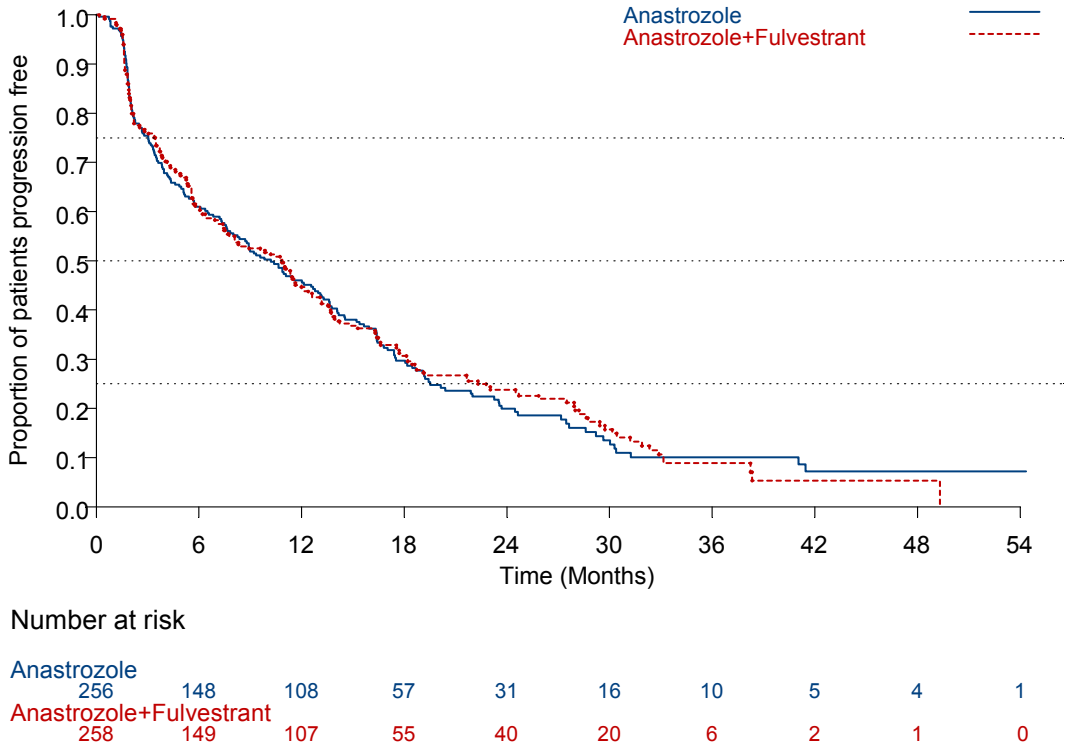
At the data cut-off date, there had been 400 progression events and the median TTP was 10.8 months for the fulvestrant + anastrozole arm and 10.2 months for the anastrozole arm (Table S3 and Figure S1).

Table S3 Summary and analysis of TTP: full analysis set

	Fulvestrant + anastrozole arm n=258	Anastrozole arm n=256
Number of patients with progression (%)	200 (77.5)	200 (78.1)
Median TTP (months)	10.8	10.2
Primary TTP analysis (log-rank test) results		
Hazard ratio[a] (95% confidence interval)	0.99 (0.81 to 1.20)	
p-value	0.91	

a A hazard ratio <1 indicates that the fulvestrant + anastrozole arm was associated with a longer time to progression than the anastrozole arm.

Figure S1 Kaplan-Meier plot of TTP: full analysis set



The log-rank analysis indicates that there was no statistically significant difference between the two treatment arms in terms of TTP. Consistent results were obtained with the Cox proportional hazards regression model. Additionally, results of a global interaction test ($p=0.83$) indicate that overall the treatment effect was consistent across the four sub-groups assessed. Results for the secondary efficacy variables support those for the primary variable, and are presented in the main study report.

As soon as possible after the results of the primary analysis had been communicated to study investigators, any patients ongoing on study treatment were continued on anastrozole only, irrespective of which treatment arm they had been randomised to.

Summary of safety results

The observed safety profile of anastrozole was consistent with existing knowledge. Fulvestrant in combination with anastrozole resulted in an approximate doubling of the incidence of hot flushes over that for anastrozole alone (63/256 patients [24.6%] vs. 35/254 patients [13.8%], $p<0.01$). There were more patients in the fulvestrant + anastrozole arm who had an AE with outcome of death (11/256 patients [4.3%], vs. 5/254 patients [2.0%] in the anastrozole arm), with slightly increased numbers of cardiac failure (3 vs. 0, respectively) and pneumonia (2 vs. 0, respectively) AEs. These numbers were not statistically significant according to retrospective Fisher's analysis. A thorough review of the individual cases did not reveal causal association between study therapy and these events. All of these patients had concurrent conditions, risk factors, or medications that could have put them at increased risk for developing the events with outcome of death. There was no relevant clustering of SAEs or of AEs leading to treatment discontinuation in the fulvestrant + anastrozole arm. No new safety concerns regarding fulvestrant + anastrozole combination therapy were identified from the clinical laboratory results, and no clinically relevant trends were evident from the vital sign and physical examination data.