AstraZeneca

Clinical Study Report Synopsis

Drug Substance	ZD 9238
Study Code	9238GR/0002
Edition Number	1.0
Date	18 December 2011

An open, non-randomised multicentre phase II study to assess the efficacy and tolerability of a 250 mg monthly dose of i.m. applied Fulvestrant for the treatment of recurrent or metastatic endometrial carcinoma

Study dates: First subject enrolled: 18 December 2002
Last subject last visit: 03 February 2011

Phase of development: Therapeutic exploratory (II)

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

Study centre(s)

N=9 study centres in Germany.

Publications

Emons G; Günthert A; Thiel F; Camara O; Strauss H; Breitbach GP; Kölbl H; Reimer T; Finas D; Rensing K. Results from a phase II study (AGO-Uterus 5) to assess the efficacy and tolerability of fulvestrant 250 mg/month as treatment of recurrent or metastatic endometrial carcinoma. J Clin Oncol 2009, 27 (15S): 5532 (285s)

Objectives and criteria for evaluation

The following objectives and related outcome variables were analysed:

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
Efficacy of a monthly application of Fulvestrant (250 mg intramuscular) in patients with recurrent or metastatic endometrial carcinoma	Clinical tumour response (complete remission and partial response) after 3 injections of Fulvestrant as determined by radiological, ultrasound - or clinical examinations	Efficacy
Secondary	**Secondary**	
Time to progression	Time from first application of study medication to diagnosis of progression	Efficacy
Median survival	Time from first application of study medication to death	Efficacy
Safety and toxicity of Fulvestrant	Assessment of the frequency of grade I-IV haematological and non-haematological toxicities	Safety
Quality of life	Patients' self-evaluation using the FACT-En questionnaire (Version 4)	Patient reported outcome

Study design

Open, non-randomised multicentre phase II study to investigate the efficacy and tolerability of a monthly i.m. application of 250 mg Fulvestrant as a first line endocrine therapy in patients with recurrent or metastatic endometrial carcinoma.

Target subject population and sample size

Postmenopausal patients with histologically confirmed diagnosis of recurrent or metastatic endometrial carcinoma (stage FIGO IVB and not to be controlled by surgery or radiation), whose tumours were progesterone receptor positive and who did not suffer from 'high-risk metastasis' were included in the study.

The sample size was calculated according to the optimal 2-step design for phase II studies by Simon et al., 1989 with the possibility of an early termination of the study in case of unsatisfactory response of the patients to the therapy. The study was to be stopped if less than 2 of the first 12 evaluable patients showed a response to Fulvestrant. If two or more of the first 12 evaluable patients responded to the therapy, which was the case in this study, another 23 patients had to be included.

Accordingly, the actual number of patients in this study was N=35.

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

Fulvestrant (ZD 9238), manufactured by AstraZeneca GmbH) is a pure anti-estrogen with high affinity to the estrogen-receptor.

Fulvestrant was made up in a 5%-solution containing ethanol, benzyl alcohol, benzyl benzoate and castor oil and was provided in vials containing 250 mg in a total volume of 5 ml corresponding to a concentration of 50 mg/ml. Patients received one 250 mg Fulvestrant - injection i.m. (m. gluteus maximus) per month (28 days ± 3 days).

Duration of treatment

Patients with complete remission (CR), partial response (PR) or stable disease (SD) received Fulvestrant 250 mg monthly until progression or until other reasons (e.g. non-compliance, protocol violations, withdrawal of Informed Consent, appearance of an intolerable serious toxicity) required discontinuation of study treatment.

Statistical methods

According to the provisions made by the optimal 2-step design an interim analysis with respect to the primary study objective was performed after the data of 12 patients were evaluable. Following the results of this analysis, a decision was made to continue with the study until completion of the pre-planned sample size (N=35).

Amendment 2 to the protocol states that the final data analysis will also include the data of patients on-treatment after the pre-determined data-cut-off-date. This was the case for 2 patients.

Descriptive statistics were used to summarize patients' data at baseline and throughout the therapy. The primary endpoint was calculated as follows:

cResponse Rate = (cComplete Remission + cPartial Response)/number of evaluable patients

Number and percentage of patients with complete remission, partial response, stable disease and overall response are presented. Additionally 95% confidence intervals are used to describe

the stability of the estimate of all desired response rates. To evaluate time to progression and median survival, a Kaplan Maier analysis is used including 95% confidence interval for median time.

Statistical analyses are based on the all-subjects-treated population (AST), the intention-to-treat population (ITT), and the per-protocol population (PP), with the primary analysis performed on data of the ITT population.

Subject population

Thirty-five patients were screened and treated with Fulvestrant in 9 centres in Germany and allocated to the different analysis populations as follows:

Table S2 Number of patients in the different analysis populations

Analysis population	Number of patients (%)
Enrolled patients	35 (100.0)
Patients included in the AST population	35 (100.0)
Patients included in the ITT population	26 (74.3)
Patients included in the PP population	24 (68.6)

Nine patients were excluded from the ITT population due to the occurrence of major events (e.g. progression of desease, death or protocol deviations) before restaging could be performed. Relevant demographic and baseline characteristics of the AST population were: mean age of 69.5 (±8.7) years with a diagnosis of endometrial carcinoma 2.6 years (mean) before enrolment. At first diagnosis, most frequent histological subtype was endometrioid (N=25, 71.4%), followed by uterine papillary serous (N=5, 14.3%), mucinous (N=1, 2.9%), mixed (N=2, 5.7%), and undifferentiated/unknown (N=1, 2.9%). Tumours were of grade 2 (N=18, 51.4%) or grade 3 (N=10, 28.6%) in most cases. Estrogen and progesterone receptor status was positive in 27 (77.1%) and 24 (68.6%) patients, respectively. Metastases or recurrence of tumour was first diagnosed 9.9 months (mean) before enrolment. At study start, local recurrence of tumour lesions was identified in 13 patients (37.1%), distant metastases were identified in chest (N=17, 48.6%), lymph nodes (N=11, 31.4%), liver (N=5, 14.3%), bone (N=3, 8.6%) or other (N=11, 31.4%).

Summary of efficacy results

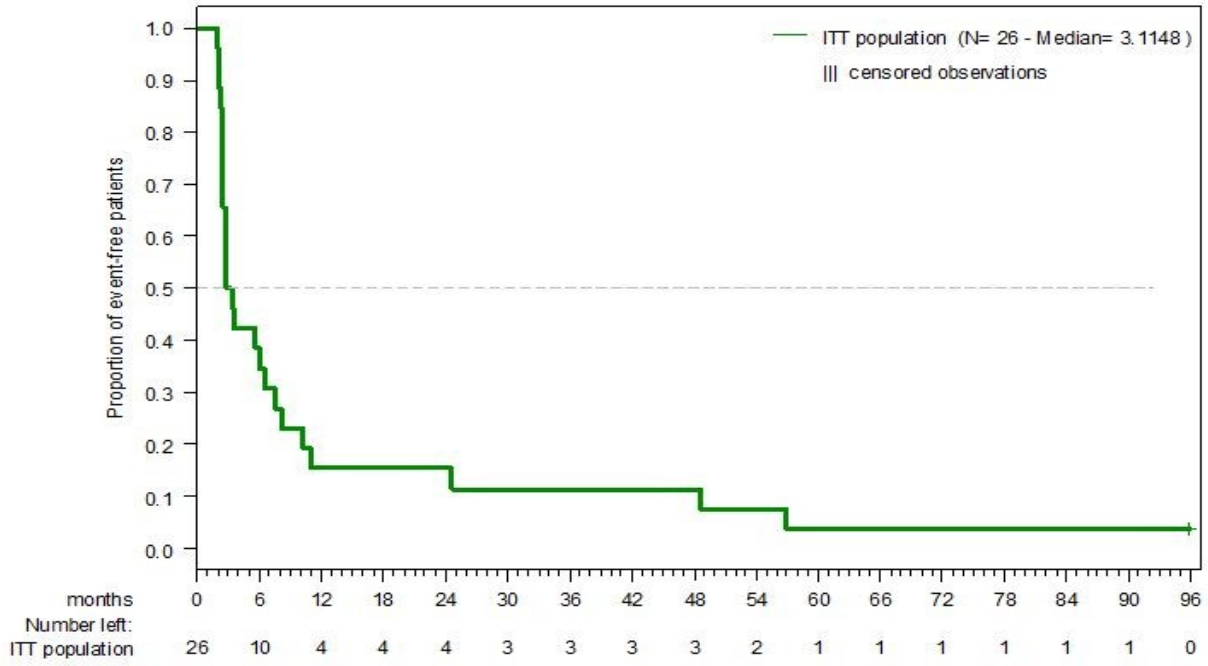
Objective response rate as the primary clinical outcome variable was determined by an independent, expert panel according to WHO response criteria. In one patient a correction had to be made and the original assessment of partial response was changed to progressive disease.

Table S3 Objective response rate following treatment with Fulvestrant, 28 ± 3 days after third treatment (ITT population, N=26)

	Response (ITT population),	
Parameter	**Number of patients**	**%**
Best tumour response		
Complete remission	0	0.0
Partial response	4	15.4
Stable disease	8	30.8
Progressive disease	14	53.8
Total	26	100.0
Objective response		
Yes	4	15.4
No	22	84.6
Total	26	100.0

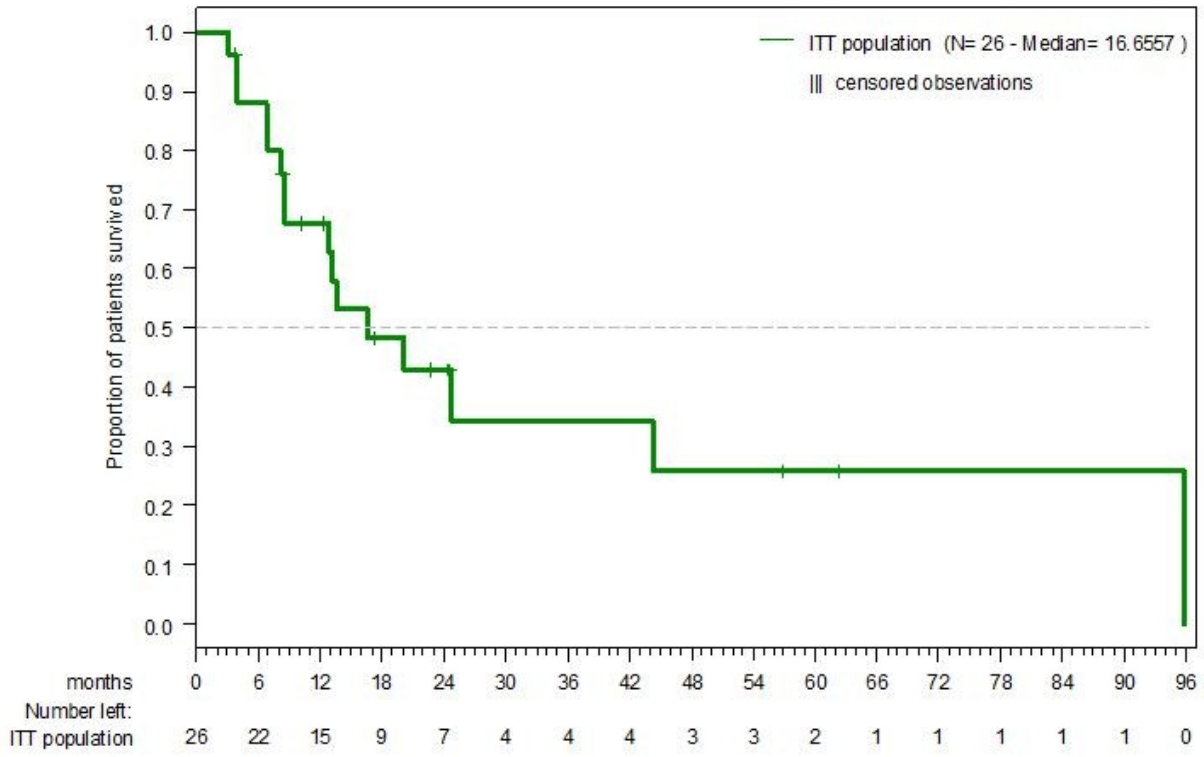
Four patients of the ITT population had a partial response (15.4%) and 8 patients had stable disease (30.8%). Accordingly, the rate of objective response following treatment with Fulvestrant was 15.4%. Time to progression as a secondary parameter of efficacy was 3.1 months (median, 95% CI: 2.6-6.5, ITT population).

Figure S1 Time to progression – Kaplan-Meier plot (ITT population, N=26)



Overall survival as a further secondary parameter of efficacy was 16.7 months (median, 95% CI: 8.6-44.4, ITT population).

Figure S2 Overall survival – Kaplan-Meier plot (ITT population, N=26)



Primary and secondary efficacy results derived from AST and PP patient populations did not relevantly differ from the ITT patient population analysis.

Quality of life was assessed by the patients using the FACT-En questionnaire (Version 4). The following results were obtained for the total score (information on subgroups of the questionnaire: physical well-being, social circumstances, mental well-being, functional scores and general scores is included in the CSR) with a higher scale score representing a higher level of well-being:

Summary of safety results

The safety analysis was based on the AST population. During the study period a total of 32 patients (91.4%) experienced 169 adverse events. Eleven patients (31.4%) had at least one serious AE, 4 of them with fatal outcome.

Table S4 Summary of patients with adverse events (AST population, N=35)

Patients with	Number of patients (%)	Number of adverse events
At least one AE	32 (91.4)	169

Patients with	Number of patients (%)	Number of adverse events
At least one SAE	11 (31.4)	22
At least one SAE related to study treatment	1 (2.9)	1
AE causing premature discontinuation	2 (5.7)	2
AE severity grade 3-4	10 (28.6)	20
AE related to study treatment	13 (37.1)	22
Fatal outcome caused by AE	4 (11.4)	4

Most frequently documented adverse events by system organ class (SOC) were gastrointestinal disorders (N=17 patients, 48.6%), general disorders and administration site conditions (N=15, 42.9%), respiratory, thoracic and mediastinal disorders (N=13, 37.1%), and vascular disorders (N=11, 31.4%). Most frequently documented preferred terms were nausea (N=9 patients, 25.7%), fatigue (N=8, 22.9%), and dyspnoea (N=7, 20.0%). Most frequently documented AEs related to study treatment were nausea (N=4 patients, 11.4%) and fatigue (N=3, 8.6%). Bone pain and vaginal haemorrhage led to discontinuation of study treatment in 2 patients (5.7%).

One of the 22 SAEs was related to study therapy (vomiting), 1 led to discontinuation of treatment (vaginal haemorrhage) and 4 were of fatal outcome (aspiration, depression, pulmonary embolism, and general physical health deterioration).