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Abstract

Purpose: Response to fulvestrant and survival in postmenopausal hormone-sensitive advanced breast cancer was investigated within a non-randomized, In-Practice Evaluation Program, with the aim of optimizing treatment decisions.

Methods: 848 patients (median age 64 years; 52% co-morbidity; 78% prior palliative therapy; median 4 prior regimens) received monthly fulvestrant injections (250 mg/month) and were followed-up three-monthly for 9 months.

Results: Clinical benefit (PFS ≥24 weeks) occurred in 532/848 (62.7%); stable disease (SD) in 627/848 patients (74%), including 62 complete and 177 partial responses. Best response was delayed in 115 patients. Estimated 9-month overall survival (OS) was 89%; 9-month event-free survival (EFS) was 71%. Indicators of disease aggressiveness affected response and survival, but number of fulvestrant cycles was the key OS and EFS determinant. Patients with SD at 3 months benefitted from continued fulvestrant. Excluding deaths, 7 serious adverse events occurred (none attributable to fulvestrant). No new or unexpected safety issues arose; 90% of patients and physicians rated fulvestrant tolerability as “very good” or “good”.

Conclusions: In the largest prospective, fulvestrant-treated cohort to date, advanced breast cancer patients achieving SD or better after 3 months of treatment gained survival benefit by prolonging fulvestrant therapy - independent of disease and treatment history.

Introduction

In advanced breast cancer, control of disease progression by endocrine rather than by cytotoxic agents induces fewer side effects and contributes to quality of life. However, in initially hormone-sensitive tumors, tamoxifen resistance [1-3] develops via estrogen-receptor (ER) agonistic effects, e.g. in bone or endometrium; increased tumor-cell sensitivity developing during long-term estrogen deprivation also promotes aromatase inhibitor (AI) resistance [4].

Fulvestrant (Faslodex®, AstraZeneca) is an ER-antagonist with no known agonistic effects [5, 6]. Fulvestrant binds to the ER, blocks its function, causing rapid degradation of the ER, reduces subsequent progesterone receptor (PgR) expression [5], and inhibits ER-mediated gene transcription. This distinct mode of action results in a reduced risk of cross-resistance with other endocrine agents [7-12]. The two registration phase-III trials in postmenopausal patients with advanced breast cancer (ABC) following antiestrogen therapy showed that response and progression-free survival (or time to progression, TTP) of fulvestrant and anastrozole were similar [13-15]. In ABC, fulvestrant was equally effective when compared to the steroidal AI exemestane after non-steroidal aromatase inhibitor therapy [16] and also equally effective to tamoxifen in patients without prior endocrine therapy [17]. In vitro, fulvestrant inhibits growth of ER-positive breast cancer cells [18], reduces ER levels [10], and inhibits estrogen-regulated proteins such as PgR, pS2, and Cathepsin D more strongly than tamoxifen [19].

This paper evaluates response to fulvestrant and survival (EFS and OS) in postmenopausal patients with advanced breast cancer receiving fulvestrant within an “In Practice Evaluation Program” (IPEP). The large (n=848) and clinically representative collective provides sufficient statistical power to model “predictive” marker-treatment interactions and detect uncommon serious adverse events (SAE). The IPEP framework also allows estimation of the frequency of delayed fulvestrant responses (beyond 2nd examination/later than three months) and the probable consequences of prolonging/discontinuing therapy (based on course of response). These are central issues of clinical concern that have not been adequately addressed and which do not necessarily require a randomized study design.

Methods

Patients and treatment

Postmenopausal patients (n=848) with locally advanced or metastatic breast cancer received fulvestrant (Faslodex®, AstraZeneca) 250mg via once-monthly intramuscular injections. The study was prospectively documented from 9/15/2004 (first patient in) until 3/28/2007 (last patient out); 278 office-

based gynecologists participated. All patients were classified hormone receptor positive; HER2 amplification (coded as IHC3+ or FISH+ vs. neg./unknown) was not a selection criterion [20].

Of the 848 included patients, 818 (96.5%) had undergone primary surgery, 748 (88.2%) had received systemic adjuvant therapy, and 760 (89.6%) had received prior hormonal therapy. First examinations (beginning 1/29/2004) were documented retrospectively in 159 patients; in 69 of these cases, second examinations were also reported retrospectively. A total of 84 patients died before completing the study.

Assessments and analyses

Baseline (1) and follow-up examinations (2, 3, 4) were scheduled at 3-month intervals for 9 months; within the IPEP, longer surveillance times also occurred. Response was categorized by individual physicians according to current guidelines (www.ago-online.de). AEs and SAEs were collected at each examination and coded according to MedDRA version 9.0. Multiple AEs occurring in a given patient within one organ system were counted once.

Baseline disease characteristics and detailed therapeutic history were documented; number and type of prior endocrine regimens, chemotherapy regimens, total (endocrine plus chemotherapy) regimens, and further information were computed from this data; numbers include adjuvant plus palliative therapies unless otherwise stated.

Concomitant medications counted as one line of treatment; interrupted regimens also counted only once. Binary (1/0) indicators were defined for “any past AI”, “any past tamoxifen”, and “past AI with no tamoxifen”. Binary indicators were also defined describing presence or absence of metastatic disease at the following sites: bone, visceral, soft tissue, distant without bone, only bone, any distant, locally advanced and “other” (unknowns classified absent). The total number of fulvestrant injections received was denoted “fulvestrant cycles”; a binary indicator was defined using the media number of cycles (>7 vs. $\leq$7 cycles, representing 6 months of treatment versus shorter).

Statistical analyses

Endpoints were overall survival, event-free survival, and best response to fulvestrant. Duration of overall survival (OS) and event-free survival (EFS) were defined from the time of first fulvestrant injection. To calculate the event-free survival interval, “events” refer to premature termination due to SAE, disease progression (PD), or death. Patients terminating for other reasons were considered right-censored. Response proportions are given with respect to the entire study population (n=848).

The impact of various factors on EFS and OS was determined using Cox proportional hazards models (stepwise forward unless otherwise stated); OS was estimated using the product-limit method (log-rank test). Weibull distributions were also fitted to estimate median OS and EFS when most patients were censored before median survival was reached in Kaplan-Meier estimates.

Chi-square or Fisher's exact test were used to analyze relationships between categorical variables. The T-test (or the Mann-Whitney U-test) was used to assess relationships between binary and metric variables. Spearman (rank) correlations are denoted R_S. Responses were coded on an ordinal scale: 0=unknown, 1=PD, 2=stable disease (SD), 3=partial response (PR), 4=complete response (CR). Binary (1/0) efficacy indicators were defined for "remission" [PR or CR vs unknown, PD or SD] and "benefit" [PR, CR or SD vs PD or unknown]. (The term CB is reserved for benefit persisting ≥24 weeks). Odds ratios (OR) characterizing the impact of various factors on binary indicators were estimated by univariate and multiple logistic regression analyses. Area under receiver operating characteristic (ROC) curves was also used to characterize the impact of these factors.

Metric variables – age, body mass index (BMI), and total number of fulvestrant cycles, were entered in logistic (or Cox) regression analyses as fractional population rank. Corresponding OR and hazard ratios (HR) were interpreted accordingly.

SAS and SPSS were used to perform these statistical analyses; 95% confidence intervals were reported; all p-values are two-sided.

Results

Patient characteristics and treatment

Baseline characteristics are shown in Table 1. Number of prior chemotherapy lines (but not endocrine therapy) was associated with the presence vs absence of metastases: visceral (2.2 lines vs. 1.5 lines, $p < 0.001$), soft tissue (2.1 lines vs. 1.7 lines, $p = 0.003$), and other distant metastases (1.8 vs. 1.6, $p < 0.001$). Median number of fulvestrant cycles was 7 (4-9; 25^{th} - 75^{th} percentile). Benefit was observed in 627/848 patients (74%), including 62 (7.3 %) complete and 177 (21%) partial responses.

Initial predictors of response

Chemotherapy pretreatment was unfavorably associated with best response to fulvestrant ($p = 0.017$; Fisher), with higher progression (18.6% : 11.8%) and lower CR (7.2% : 13.7%) rates; patients with prior endocrine therapy had higher response (PR+CR) rates than those without (34.5% : 17.1%; $p = 0.002$).

A response during last treatment significantly predicted response to fulvestrant: OR = 3.01 (2.15-4.23 , p <0.001); R_S = 0.3 (p <0.001) (Table 2).

Course of response

Best response was delayed (beyond 2nd examination) in 115 patients (see Table 2). Remarkably, 18% (84/459) of patients with stabilization at 2nd examination subsequently achieved partial or even complete remission; of those with >7 cycles (about 64%), 26% improved, compared to 4.8% of the others (p <0.001).

Association between number of fulvestrant cycles and response

Number of fulvestrant cycles were strongly associated with benefit [PR, CR, SD], as one would expect. Treating response as an ordinal variable, number of fulvestrant cycles also correlated with response (R_S = 0.42, p <0.001). Dichotomizing the treatment variable (>7 vs. <=7 cycles) yielded log(OR) = 3.8 (3.1-4.5); fractionally ranking fulvestrant cycles yielded log(OR) = 9.8 (8.4-11.2), implying, e.g., OR >100 for "benefit" in a patient receiving nine fulvestrant cycles compared to four. An ROC curve for "benefit" as a function of cycles had AUC = 0.93 (0.90-0.95).

Obviously, this association partially reflects the fact that patients with favorable outcome will be more likely to continue fulvestrant. However, it is truly noteworthy that „fulvestrant cycles" strongly predicted subsequent remission [log(OR) = 4.1 (2.9-5.4)] in the key subgroup (n=459) of patients with SD at 2nd examination.

Overall survival

Overall, 84 deaths were recorded, 66 within 9 months. Estimated 9-month OS (including censoring) was 89.1% (86.5%-91.8%); median OS was estimated at 26 months (Weibull fit). OS was strongly associated with best response to fulvestrant [HR=0.3 (0.2-0.45) per ordinal level] (Figure 1).

In univariate models, higher number of fulvestrant cycles, fewer previous therapy lines, better response to last therapy, and higher BMI were favorable for OS; locally advanced disease, visceral or exclusively bone metastases were unfavorable (Table 3, left).

In multivariate analysis, fulvestrant cycles dominated all other factors in the whole collective (Table 3, top right) and in subgroups (SD at second examination, CB by second examination). Patients with SD at 2nd examination who received >7 fulvestrant cycles had an HR of 0.120 (0.054 - 0.267) for OS, with visceral metastases having an unfavorable effect on outcome.

As the number of fulvestrant cycles was determined not by randomization, but by course of response, Table 3 (bottom right) also presents multivariate analyses of OS, restricted to factors known initially

(i.e., excluding fulvestrant cycles). All significant univariate factors were independent multivariate predictors for OS in this analysis.

Disease progression and event-free survival

Overall, 532/848 (uncensored) patients had CB, i.e., were known to be progression-free for ≥24 weeks; 167 progressed (one with subsequent response) or died within 24 weeks. Events were recorded in 265/848 patients. Median EFS was 12 months (Weibull and Kaplan-Meier estimators).

In addition to number of fulvestrant cycles, earlier therapy line and negative PgR status appeared to be independently favorable for EFS (Table 4). There were no significant associations between EFS and BMI, locally advanced disease, bone metastasis (only), line of endocrine therapy, line of AI therapy, soft tissue metastasis, breast cancer survival, HER2 status or ER status. Since PgR status entered the multivariate model despite lacking univariate significance, receptor-treatment interactions were tested for: an interaction between PgR status and number of fulvestrant cycles was detected (HR = 0.22). Noting HR = 2.85 for PgR status and HR = 0.06 for number of fulvestrant cycles, and comparing with the other multivariate EFS model, the implication is that while EFS generally improved with prolonged fulvestrant treatment, PgR-positive patients benefited most. The PgR-positive and PgR-negative groups were well-balanced in terms of the number of fulvestrant cycles received; qualitatively similar findings were observed grouping “unknown” with positive PgR status. No interactions were detected involving either ER or HER2 status.

In the subgroup of patients with SD by 2nd examination (3 months), patients receiving >7 cycles had a HR of 0.479 (0.294 - 0.782) for EFS, with visceral metastases having an unfavorable impact.

Safety and Tolerability

Seven SAEs were recorded, none of which were judged to be attributable to fulvestrant. Two SAEs resulted in subsequent death (pulmonary embolism, pneumonia); one non-fatal stroke and one non-fatal heart attack also occurred. Table 5 summarizes all non-serious AEs occurring among the 848 patients included in this study. No new or unexpected safety issues arose. Of the 84 patients who died during this study, heart failure/insufficiency was explicitly cited in the deaths of six patients; one of these six patients had suffered a previous AE attributed to fulvestrant (urticaria). In all, nine of the 84 patients who died had a documented AE; of these, the only AE attributed to fulvestrant was the aforementioned urticaria. Breast cancer was the reported cause of 69/84 deaths; of the remaining 15 deaths, the reported causes were as follows: organ failure (heart/cardiovascular, kidney, liver, lungs/pneumonia, multiple) and general (general worsening, cachexia, unknown); there was no evidence that any of the deaths were attributable to fulvestrant.

Treatment tolerability was assessed by patients and physicians for both the patient's last breast cancer therapy and for fulvestrant (Table 6). Patient and physician ratings were strongly correlated (R_S > 0.87; p <0.001), with slightly higher physician-rated tolerability. Very good tolerability was reported in 41.4% to 47.5% of patients receiving fulvestrant (46.7% to 51.6% of physicians) compared to 20.0% for last therapy (18.0% of physicians). The percentages of patients (or physicians) reporting "insufficient" tolerability of fulvestrant was ≤1.5% and the percentages reporting "good" or "very good" exceeded 90%.

Almost half of all patients reported an improvement in tolerability of fulvestrant compared with their last therapy (Table 7). Tolerability at 2nd examination was also positively associated with EFS: Combining the "good" and "very good" categories, the HR associated with each degree of improvement (e.g., "insufficient" → "satisfactory" etc.) was 0.570 (0.425 - 0.765, P <0.001). This association may be partly attributable to the correlation (R_S = 0.14, P <.001) between tolerability (ordinal scale) and number of fulvestrant cycles; in the metastatic setting, patient-reported tolerability may also reflect palliative benefits and thus quality of life.

Discussion

Due to its efficacy even after failure of other endocrine agents, fulvestrant represents a valuable treatment option for patients with advanced breast cancer whose disease is not immediately life-threatening [7-12]. Previous results [21] demonstrated the importance of allowing sufficient time (>2 months) for evaluating response to fulvestrant – for example, a patient may still respond despite intermittent rises in CA15.3. In phase III trials, time to response was 3.1 months for Fulvestrant (range 0.9 – 33.1 months) [22]. The present single-arm study comprises the largest available data set for studying fulvestrant in advanced breast cancer, providing more power for subgroup and multivariate interaction analyses.

Analysis of the degree to which response and survival are positively influenced by fulvestrant therapy requires careful consideration of the present study design: Since this is an observational study, a "feed-back" process is possible, i.e., duration of fulvestrant therapy is influenced by response, so that a cause-and-effect or dose-response relationship cannot be inferred. The "best" responders (PR or CR within 3 months) tended to prolong fulvestrant treatment, receive more cycles, and benefit most. Patients without benefit by 3 months tended to discontinue fulvestrant and almost never improved even if they had subsequent fulvestrant treatment.

However, in “intermediate” responders - the 459 patients with SD within three months, but not yet partial or complete response - the decision to prolong fulvestrant therapy was split (64% received >7 cycles). It truly noteworthy that in this subgroup, number of fulvestrant cycles (i.e., continuation of fulvestrant after SD at 3 months) was strongly associated with subsequent response (OR ≈ 60). For example, a remission occurred in approximately one-quarter of intermediate responders receiving >7 fulvestrant cycles, compared with about one-twentieth of those receiving ≤7 cycles. Moreover, intermediate responders receiving >7 cycles had a substantial advantage in OS and EFS. The survival benefit of receiving more fulvestrant cycles was almost as strong in patients with (only) SD by 3 months as it was in the overall population. Summarizing, in the subgroup of “intermediate responders,” the inference of a positive dose-response relationship does appear to be the most likely explanation of the data.

Considering the substantial pre-treatment and other patient characteristics, the estimated 9-month OS of 89% (median OS ≈ 26 months) compares favorably with the 24-month median OS considered typical for patients metastatic breast cancer. Estimated median EFS was 12 months – which also gives a conservative estimate of median TTP. These estimates underline the benefits of fulvestrant for patients with hormone-sensitive, metastatic breast cancer.

Seven SAEs were recorded, none of which were attributable to fulvestrant; and no new or unexpected safety issues arose. An advantage of the intramuscular mode of administration of fulvestrant is that compliance is not an issue. Over 90% of both patients and physicians rated fulvestrant tolerability as “very good” or “good” throughout the study. Moreover, almost half of all patients reported improved tolerability of fulvestrant compared with their last therapy. It is also noteworthy that tolerability was predictive of improved EFS. This relationship could be explained by the likelihood of receiving more cycles, which was strongly associated with improved EFS and OS.

A patient’s response to fulvestrant reflects multiple dynamically interacting and competing biological processes regulating cancer cell growth in that individual. Previous trials have shown that fulvestrant is active in patients with visceral metastases [23-26]. However, direct indicators and surrogates for disease aggressiveness would still be expected to exert some negative influence on response and survival. Thus, presence of visceral metastases had negative impact on OS and EFS (in all patients and in the subgroup with SD at 3 months). The (positive) association of “fewer lines of previous therapy” with EFS and OS and the (negative) association of “previous chemotherapy” with fulvestrant response could also be attributable to their association with disease aggressiveness, as evidenced by

the correlation of visceral metastases with chemotherapy. In contrast, “best response to previous therapy” was a strong predictor of response to fulvestrant, EFS and OS, but was not strongly associated with disease aggressiveness markers. This observation is consistent with results from the EFECT trial [16, 27]. Further research is required to permit a better understanding of the relationship between response to previous therapy and response to fulvestrant.

Here, for the first time, a predictive interaction between PgR status and number of fulvestrant cycles was identified in the multivariate analysis of EFS. A previous report [20] based on a study of 155 metastatic breast cancer patients did not find an interaction of this type. However, the effect size observed here would not have been significant in a 155-patient study, because the confidence interval for log(HR) would have been about 2.3 times wider, thus overlapping zero; hence the apparent difference could be attributable to increased power. Interpretation of the predictive interaction requires consideration of the multivariate model (Table 4) as a whole: In patients receiving fewer fulvestrant cycles, EFS was worse in PgR-positive than in PgR-negative patients (controlling for line of therapy and presence of visceral metastases). In the whole collective, EFS improved with number of fulvestrant cycles, but the observed benefit was greater in PgR-positive patients - more than enough to compensate for the “disadvantage” of PgR-positivity.

Considering the biological role of PgR regulation in fulvestrant efficacy, the possible increased benefit in patients with positive PgR status could provide an interesting hypothesis for future controlled studies (with centralized receptor determination). In view of the association of molecular types with clinical outcomes [28], we note that the predictive value of presence or absence of PgR could also hint at a fundamental difference between luminal A vs. luminal B type tumors even in the metastatic context.

While factors and surrogates for disease aggressiveness (e.g., visceral metastases, previous chemotherapy, etc.) were negatively associated with response, patients responding at all (stabilization or better) by three months had substantial survival benefit from continued fulvestrant treatment. This statement applies to patients with previous chemotherapy, aromatase inhibitor therapy (whether pre-treated by tamoxifen or not). Notwithstanding, our data suggest that it would be prudent to plan therapy strategies in advanced and metastatic breast cancer by providing fulvestrant as an additional endocrine therapy line to patients at a sufficiently early stage so as to improve the chances of responding. This strategy is also supported by recent health economic data [29].

In this IPEP, fulvestrant therapy was usually terminated in patients with PD at three months and continued in patients with remission (CR or PR) at this time. Current clinical practice is supported by our data in these patient groups. However, in patients achieving “only” SD by three months (who constituted the majority) fulvestrant therapy was terminated in over 30% of cases. The present results suggest that continuation of fulvestrant therapy in all patients achieving SD at three months is likely to benefit these patients in terms of (possibly delayed) remission, quality of life, and survival. It would be valuable to validate these findings in the ongoing clinical fulvestrant trials[30, 31]. Moreover, recent trial results with a higher dose of fulvestrant (500 mg) suggest that the observed effects in responders may even be greater when fulvestrant is administered at the higher dose [32, 33].

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Tables

Table 1 Patient baseline characteristics: a) Distributions of metric variables; b) Tumor characteristics: metastases and hormone receptors

a)

Metric variables	Total		
	Mean	SD	N valid
Age [years]	64.4	10.4	836
Body Mass Index [kg/m^2]	26.4	4.6	824
Survival (from original breast cancer diagnosis to study begin) [months]	93.4	68.4	788
Duration of response to last therapy [months]	18.3	19.7	575
Number of prior therapy regimens	4.0	2.1	848

b)

Sites of metastases	**Patients, n (%)**	
Category	Present	Absent or unknown
Local advanced	324 (38.2)	524 (61.8)
Any distant	796 (93.9)	52 (6.1)
Visceral	321 (37.9)	527 (62.1)
Bone	486 (57.3)	362 (42.7)
Soft tissue	161 (19.0)	687 (81.0)
Other distant metastases	133 (15.7)	715 (84.3)
Only bone	215 (25.4)	633 (74.6)
Distant without bone	252 (29.7)	596 (70.3)
Receptor status		**Patients, n (%)**
ER	Negative	27 (3.2)
	Unknown	23 (2.7)
	Positive	798 (94.1)
PgR	Negative	116 (13.7)
	Unknown	40 (4.7)
	Positive	692 (81.6)
HER2	Negative	345 (40.7)
	Unknown	333 (39.3)
	FISH +	56 (6.6)
	IHC+++	114 (13.4)

ER = estrogen receptor; PgR = progesterone receptor; HER2 = human epidermal growth factor receptor 2

Table 2 Best response (BR) to fulvestrant vs BR to last therapy, BR at second examination or BR at 3rd examination

		Best response to fulvestrant					
		unknown	PD	SD	PR	CR	Total
Best response to last therapy	Unknown	36	18	59	24	13	150
	PD	6	11	22	6	1	46
	SD	32	63	193	62	10	360
	PR	22	23	95	65	13	218
	CR	4	6	19	20	25	74
Response to fulvestrant (2nd examination)	Unknown	100	10	13	3	0	126
	PD	0	111	0	1	0	112
	SD	0	0	375	73	11	459
	PR	0	0	0	100	14	114
	CR	0	0	0	0	37	37
Best response to fulvestrant (up to 3rd examination)	Unknown	100	2	2	0	0	104
	PD	0	119	0	0	0	119
	SD	0	0	386	24	3	413
	PR	0	0	0	153	5	158
	CR	0	0	0	0	54	54
Totals		100	121	388	177	62	848

PD = disease progression; SD = stable disease; PR = partial response; CR = complete response

Table 3 Proportional hazard models for OS. Entered but not significant: age, antihormonal therapy line, bone metastases, soft tissue metastases, time since breast cancer diagnosis, HER2, PgR, ER, interactions of fulvestrant cycles with PgR, ER, HER2. **Left:** univarate. **Right:** two multivariate models (including/excluding fulvestrant)

OS	Univariate			Multivariate (fulvestrant & factors entered)		
Factors	P	HR (95% CI)	ln (HR)	P	HR (95% CI)	ln (HR)
Fulvestrant: number of cycles (fractionally ranked)	<0.001	.002 (.001 - .006)	-6.25	<0.001	.002 (.001 - .005)	-6.41
				Multivariate (excluding fulvestrant; other factors entered)		
Response to last therapy (scaled 1 to 4)	<0.001	0.71 (0.60 - 0.85)	-0.34	0.002	0.73 (0.60 - 0.89)	-0.31
BMI (fractionally ranked)	0.017	0.39 (0.18 - 0.85)	-0.94	0.021	0.39 (0.18 - 0.87)	-0.94
Line of therapy (number)	<0.001	1.17 (1.07 - 1.28)	0.16	0.023	1.12 (1.01 - 1.23)	0.11
Locally advanced disease (present vs absent)	0.007	1.63 (1.14 - 2.32)	0.49	0.007	1.68 (1.15 - 2.45)	0.52
Bone metastases only (yes vs no)	0.010	1.79 (1.15 - 2.81)	0.58	0.015	1.79 (1.12 - 2.87)	0.58
Visceral metastases (present vs absent)	0.018	1.68 (1.09 - 2.57)	0.52	0.042	1.63 (1.02 - 2.60)	0.49

HR = estimated hazard ratio; In = natural logarithm

Table 4 Upper left: Univariate hazard ratios of factors for EFS in forward stepwise Cox regression; **upper right:** multivariate model excluding fulvestrant. **Lower left:** multivariate EFS model including fulvestrant; **Lower right:** multivariate receptor interaction model by backward stepwise Cox regression

EFS	**Univariate**			**Multivariate (excluding fulvestrant; other factors entered)**		
Factors	P	HR (95% CI)	ln (HR)	P	HR (95% CI)	ln (HR)
Fulvestrant therapy: number of cycles (fractionally ranked)	<0.001	0.015 (0 .009 - 0.025)	-4.20	not entered		
Line of therapy (number)	<0.001	1.14 (1.08 – 1.20)	0.13	<0.001	1.11 (1.05 – 1.17)	0.10
Line of palliative hormonal therapy	0.003	1.18 (1.06 – 1.31)	0.16	not significant		
Palliative AI therapy	0.047	1.30 (1.00 – 1.69)	0.27	not significant		
Response to last therapy (scaled 1 to 4)	0.002	0.85 (0.77 – 0.94)	-0.16	0.002	0.84 (0.75 – 0.94)	-0.18
Visceral metastases (present vs absent)	0.001	1.52 (1.19 – 1.94)	0.42	0.013	1.41 (1.08 – 1.84)	0.34
Bone metastases (present vs absent)	0.014	1.38 (1.07 – 1.78)	0.32	not significant		
Binary PgR status (positive vs negative or unknown)	not significant			not significant		
EFS	**Multivariate (fulvestrant & factors entered)**			**Multivariate (fulvestrant, factors & receptor interactions entered)**		
Factors	P	HR (95% CI)	ln (HR)	P	HR (95% CI)	ln (HR)
Fulvestrant therapy: number of cycles (fractionally ranked)	<0.001	0.02 (0.01 – 0.03)	-4.18	<0.001	0.06 (0.02 – 0.20)	-2.90
Line of therapy (number)	0.012	1.07 (1.02 – 1.13)	0.07	0.040	1.06 (1.00 – 1.12)	0.06
Visceral metastases (present vs absent)	not significant			0.080	1.27 (0.97 – 1.66)	0.24
Binary PgR status (positive vs negative or unknown)	0.007	1.70 (1.16 – 2.50)	0.53	0.002	2.85 (1.49 – 5.46)	1.05
Interaction: binary PgR status * fractionally ranked fulvestrant cycles	not entered			0.040	0.22 (0.05 – 0.94)	-1.49

Table 5 Occurrence of non-serious adverse events during fulvestrant treatment including those reported at study end (n=848). PD was reported in 86 patients as an AE (none of which were reported as being due to fulvestrant)

Primary system organ class	Patients affected by AE	subset judged "due to fulvestrant"
General disorders and administration site conditions	52	4
Gastrointestinal disorders	30	3
Musculoskeletal and connective tissue disorders	22	1
Skin and subcutaneous tissue disorders	12	4
Respiratory, thoracic and mediastinal disorders	18	0
Nervous system disorders	16	1
Vascular disorders	17	7
Investigational procedures	6	2
Blood and lymphatic system disorders	10	0
Infections	12	1
Psychiatric disorders	8	4
Hepatobiliary disorders	11	1
Metabolism and nutrition disorders	10	0
Injuries and procedural complications	2	0
Cardiac disorders	7	0
Eye disorders	2	2
Renal and urinary disorders	4	0
Surgical and medical procedures	3	0
Immune system disorders	1	0
Reproductive system and breast disorders	1	1
Total	**244**	**31**

Table 6 Tolerability of previous therapy and fulvestrant as reported by patients and physicians

Tolerability	**Last therapy**		**Fulvestrant**					
			Examination 2		Examination 3		Examination 4	
	Patient	Physician	Patient	Physician	Patient	Physician	Patient	Physician
Very good	20.0%	18.0%	41.4%	46.7%	43.1%	47.3%	47.5%	51.6%
Good	47.0%	42.2%	48.8%	47.1%	49.4%	47.5%	46.1%	44.2%
Satisfactory	25.1%	27.5%	8.4%	5.4%	5.9%	4.4%	5.0%	3.3%
Insufficient	8.0%	12.3%	1.4%	0.8%	1.5%	0.8%	1.4%	0.9%
Number reporting	817	796	773	777	591	590	423	430

Table 7 Improvement of tolerability reported by patients from last therapy to fulvestrant at 2nd examination (n=730)

Degree of Improvement	Improvement	Patients, number (%)
-3	Very good → Insufficient	1 (0.1)
-2	Very good → Satisfactory	5 (0.7)
-1	Very good→ Good	56 (7.7)
0	Very good → Very good	310 (42.5)
1	Good → Very good	217 (29.7)
2	Satisfactory → Very good	107 (14.7)
3	Insufficient → Very good	34 (4.7)

Figure

Figure 1 OS by best response to fulvestrant; 9-month OS in each subgroup was estimated using the product limit method (p<0.001): response unknown (50%), PD (76%), SD (92%) PR (98%), CR (100%).