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CLINICAL TRIAL

# The Austrian fulvestrant registry: results from a prospective observation of fulvestrant in postmenopausal patients with metastatic breast cancer

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**Abstract** *Background* Endocrine therapy is the preferred treatment in oestrogen- and/or progesterone-receptor (ER/PgR) positive breast cancer. Fulvestrant is a pure ER-antagonist. We present results from the Austrian Fulvestrant Registry. *Methods* Three-hundred and fifty patients were included. Time to progression (TTP) was defined as primary endpoint. A multivariate analysis was performed to identify factors significantly associated with TTP. *Results* Fulvestrant was administered as first-line therapy in 26%, second-line in 49%, and third-line or beyond in 25%. TTP was median 7 months. We observed a response in 15% of patients and 41% had SD $\geq$ 6 months. First-line treatment and non-visceral metastases were associated with longer TTP. One case of pulmonary embolism was reported. Grade 3 toxicities consisted of joint pain (1.4%), nausea (1.4%) and hot flashes (0.3%). *Conclusions* Fulvestrant was effective and well tolerated. TTP was superior to other trials, due to the large proportion of first-line patients. Activity is apparently independent of Her2-status.

**Keywords** Endocrine treatment · Fulvestrant · Metastatic breast cancer · Oestrogen-receptor

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## Introduction

Endocrine therapy is the most widely applied treatment in oestrogen-receptor (ER)-and/or progesterone-receptor (PgR) positive early and advanced stage breast cancer. As metastatic disease is incurable, treatment is essentially palliative. The aim therefore remains a reduction of tumour-associated symptoms and prolongation of survival time, without causing further reduction in quality-of-life (QoL) [1].

As consequence, an important aspect of endocrine treatment is its potential to delay the need for cytotoxic chemotherapy. Non cross-resistant options are available, and their sequential administration may confer prolonged disease stabilization. Still, de novo or acquired (secondary)

resistance is the rule, with subsequent disease progression. Importantly, only 50% of ER-positive tumours will respond to anti-oestrogens at first presentation [2].

For three decades tamoxifen was the drug of choice. It reduces recurrence rates by a relative 47% in early breast cancer [3]. In advanced disease, response rates of 17–27% were reported [4–6]. Tamoxifen acts via a blockade of activating-function-2 (AF-2) of ER, but apparently does not inhibit AF-1 [7]. Phosphorylation at Serine 118 via growth factor signalling may confer oestrogen-independent receptor activation, with subsequent tamoxifen resistant tumour growth [8, 9].

A newer class of drugs, aromatase inhibitors (AIs), act through a suppression of plasma oestrogen concentrations via inhibition of aromatase, an enzyme responsible for synthesising oestrogens from androgenic precursors [10]. Randomized clinical trials in early and advanced breast cancer have demonstrated that third generation AIs have equivalent or superior efficacy when compared to tamoxifen [11]. Less is known about possible mechanisms of resistance. A recently published paper however suggests that a transition of ER-positive tumour cells from an AI-responsive to a resistant stage is accompanied with activation of growth factor signalling pathways, particularly the MAP-Kinase cascade [12].

Fulvestrant, the long-acting formulation of ICI 182,780, acts as pure ER-antagonist. It binds ER with a 100-fold higher affinity than tamoxifen [13]. Once bound, ER dimerization and nuclear translocation is inhibited [14], thus causing accelerated degradation of the ER protein [14, 15]. In difference to tamoxifen, fulvestrant blocks both activating functions, thereby effectively abrogating oestrogen dependent gene transcription [15, 16]. Furthermore, fulvestrant blocks nuclear as well as cytoplasmatic and membrane-bound ER, the latter two considered responsible for the ER/growth factor crosstalk [15, 17, 18]. In consequence, it was suggested that fulvestrant might be active also in Her2-positive disease. This is supported by preliminary clinical data [19, 20].

In two randomized phase III trials, fulvestrant was compared to anastrozole in postmenopausal women with hormone-sensitive breast cancer progressing on prior endocrine therapy [21, 22]. A prospectively planned combined analysis demonstrated similar efficacy of the two drugs [23]. Those data were confirmed in a number of recently published observations [24–26].

Here, we present results from the Austrian Fulvestrant registry. The program enabled 53 participating Austrian centres to contribute patients in order to analyze routine fulvestrant use. Noteworthy, this sample has a high proportion of patients older than 65 years, and a quarter of patients received fulvestrant as first-line therapy following adjuvant treatment with tamoxifen or AIs.

## Patients and methods

Data were collected from the Austrian Fulvestrant Registry. Fifty-three centres contributed information relating to demographics, disease history, prior cancer treatment, and fulvestrant therapy. Data were processed at the Medical University of Vienna, Vienna, Austria. This prospective observational study was conducted in accordance with the ethical regulations of the Medical University of Vienna.

### Patients

An overall of 350 consecutive patients treated with fulvestrant at 53 Austrian centres were included from March 2004 until May 2007 and followed prospectively. All patients are currently evaluable for toxicity and response. Data were analyzed as of December 2007.

All patients were postmenopausal women with ER-positive and/or PgR-positive disease who had failed at least one prior endocrine therapy, either as adjuvant treatment or for the treatment of advanced disease. Menopausal status was assessed clinically (amenorrhoea >1 year) and serologically (serum oestradiol within the postmenopausal range [<25 pg/ml], and serum follicle-stimulating hormone within the postmenopausal range [25.8–134.8 mU/ml]).

All patients were diagnosed with histologically confirmed metastatic breast cancer. Biopsy of metastatic lesions was not required in the protocol. Criteria for inclusion were as follows: ER- and/or PgR-positive metastatic breast cancer, postmenopausal status, Karnofsky performance score ≥70, life expectancy of >3 months, adequate haematological parameters as defined by WBC count ≥3,500/μl, platelet count ≥100,000/μl, haemoglobin levels >9 g/dl, adequate hepatic (serum bilirubin <2.0 mg/dl), and renal (serum creatinine <1.5 mg/dl) functions, and written informed consent. For baseline staging evaluations, CT-scans of the chest and the abdomen, bone scan, mammography, and gynaecologic examination were mandatory, with further work-up if indicated. Due to the observational design of this study, no central radiological review was possible.

### Hormone receptor and Her2 status

ER and PgR status were assessed by immunohistochemistry (ERα antibody, clone 1D5, Dako A/S, Glostrup, Denmark; and PgR antibody, Dako A/S, Glostrup, Denmark). Receptor expression was estimated as the percentage of positively stained tumour cells. Results were given as +, ++, +++ positive staining or negative staining, with a cut-off value of <10% positive tumour cells.

Her2 status was assessed with the Herceptest® (Dako A/S, Glostrup, Denmark) or dual colour fluorescent in situ

hybridization (FISH; PathVision® HER2 DNA probe kit, Vysis Inc., Downers Grove, IL, USA). Tumours were classified as Her2-positive if they had a staining intensity of +++ on the Herceptest®; if a score of ++ was gained, the tumours were reanalyzed using FISH. Tumours with Her2 gene amplification were deemed Her2-positive.

Although no central pathology review was available, receptor status assessment was conducted at seven academic centres with strict quality control.

### Treatment plan and patient evaluation

Time to progression (TTP) was defined as primary study endpoint; secondary endpoints were response rate (RR; CR + PR), clinical benefit rate (CBR; CR + PR + SD $\geq$ 6 months), and toxicity.

All treatment was administered in an outpatient setting. Patients received fulvestrant at the registered dose of 250 mg every 4 weeks by intramuscular injection, with treatment continuing until objective disease progression or other events that required discontinuation. At this timepoint, treatment was stopped and further therapy was initiated at the discretion of the treating physician.

Re-evaluation of patients' tumour status was performed every 3 months with CT-scans of the chest and the abdomen with additional work up if indicated. Response was assessed using World Health Organisation (WHO) response criteria. Complete response (CR) was defined as the disappearance of all measurable lesions for a minimum of 8 weeks. Partial response (PR) was defined as 50% or more reduction in sum of products of the greatest diameters of measurable lesions, no increase of lesion size and no new lesions. Stable disease (SD) was defined as less than 50% decrease and less than 25% increase without the appearance of new lesions. Progressive disease (PD) was defined as greater than 25% increase in tumour size or the appearance of new lesions.

### Statistical analysis

TTP was defined as interval from first injection until tumour progression or death of any cause while on treatment, and estimated using the Kaplan-Meier product-limit method. If a patient died without restaging for documenting disease status, TTP was measured as interval to the first day of clinical deterioration. To test differences between TTP curves, the log-rank test was used. *P* values less than 0.05 were considered to indicate statistical significance. A Cox regression model was used to evaluate factors potentially influencing TTP (age [$\leq$65 years/>65 years], PgR-status, Her2-status, visceral metastases, prior chemotherapy and treatment line [first-line versus beyond first-line]). Adverse events were recorded throughout the treatment period and were graded according to WHO toxicity criteria. Data were analysed as of December 2007. All statistics were calculated using statistical package for the social sciences (SPSS®) 12.0 software (SPSS Inc., Chicago, IL, USA).

## Results

### Patient characteristics

A total of 350 patients were accrued to this observational study. All were diagnosed with histologically confirmed invasive ductal or invasive lobular adenocarcinoma of the breast. The median age was 66 years, range 35–92 years. Fulvestrant was administered as first-line hormonal therapy in 92 patients (26%), second-line in 170 (49%), third-line in 67 (19%), and fourth-line in 21 patients (6%) respectively. Non-visceral metastases only were present in 174 patients (49%), with the reminder having also visceral involvement. One-hundred-twenty-seven patients (36%) had received prior adjuvant chemotherapy, 224 patients (64%) adjuvant endocrine treatment (tamoxifen 184, aromatase inhibitors 3, tamoxifen followed by AI sequentially 7), and 147 patients (42%) had at least one earlier line of chemotherapy for metastatic disease. Median time to disease recurrence was 38 months (range 3–336 months, 95% CI 49.72–61.77). 177/258 patients (69%) derived clinical benefit from the last palliative endocrine treatment-line before fulvestrant. Table 1 lists the characteristics of the 350 patients included.

All patients received fulvestrant and were included in the intent-to-treat population for safety analysis; as of December 2007, all individuals were also evaluable for efficacy analysis.

### Efficacy

Median TTP was 7 months, range 2–34, 95% CI 6.09–7.09. In patients receiving fulvestrant as first-line endocrine therapy, median TTP was 9 months (range 2–34, CI [95%] 8.51–9.49). Corresponding numbers were 6 months (range 3–29, 95% CI 3.77–6.23) for second-line, 5 months (range 2–67, 95% CI 3.77–6.23) for third-line, and 6 months (range 2–25, 95% CI 0.02–7.9) for fourth-line respectively (Fig. 1). The log-rang test revealed a significant difference ($P = 0.017$).

TTP in patients with non-visceral disease only was 8 m (range 3–24, 95% CI 6.99–9.01), and 6 months (range 3–29, 95% CI 4.68–7.32) in those with visceral involvement ($P = 0.023$) (Fig. 2). No significant difference concerning TTP was observed between patients deriving clinical benefit from the last hormonal treatment-line before fulvestrant and those having SD < 6 months or PD.

**Table 1** Patient characteristics

| Characteristics | Patients |
|---|---|
| Entered | 350 patients |
| Karnofsky performance score | 70–100% |
| Age (years) | |
| Median (range) | 66 years (range 35–92) |
| Patients >65 years | 158 (45.1%) |
| Oestrogen receptor-positive | 336 (96%) |
| Progesterone receptor-positive | 201 (57.4%) |
| Her2 status (IHC/FISH[a]) positive | 47 (13.4%) |
| Adjuvant chemotherapy | 127 (36.3%) |
| Adjuvant endocrine therapy | 224 (64%) |
| Adjuvant tamoxifen | 184 (82.1%) |
| Adjuvant AI | 33 (3.9%) |
| Sequential tamoxifen followed by AI | 7 (3.1%) |
| Palliative chemotherapy before fulvestrant | 147 (42%) |
| Palliative endocrine therapy | 258 (73.7%) |
| Tamoxifen | 64 (24.8%) |
| Anastrozole/letrozole | 221 (85.7%) |
| Exemestane | 78 (30.2%) |
| Others | 1 (0.4%) |
| Time to recurrence | |
| Median (range) | 38 months (range 3–336 m) |
| Treatment line | |
| First line | 92 (26.3%) |
| Second line | 170 (48.6%) |
| Third line | 67 (19.1%) |
| Fourth line | 21 (6%) |
| Metastatic sites | |
| Median (range) | 2 (range 1–4) |
| Bones/soft tissue only | 174 (49.7%) |
| Visceral involvement | 176 (50.3%) |
| Localisation | |
| Lung | 107 |
| Liver | 95 |
| Bones | 246 |
| Soft tissue | 142 |
| Others | 85 |
| More than one metastatic site | 173 (49.4%) |

[a] IHC, immunohistochemistry, Herceptest® (Dako A/S, Glostrup, Denmark); FISH, dual colour fluorescent in situ hybridisation (PathVision® HER2 DNA probe kit, Vysis Inc., Downers Grove, IL, USA)

Again, no difference was found between patients with <12 months and those with ≥12 months interval from adjuvant therapy to diagnosis of metastatic disease.

Treatment with fulvestrant produced CR in eight patients (2.3%, 95% CI 0.73–3.87), PR in 43 patients (12.3%, 95% CI 8.86–15.74), and SD ≥ 6 months in 143 patients (40.9%, 95% CI 35.74–46.05), resulting in a RR of 14.6% (95% CI 10.9–18.3) and CBR of 55.5% (95% CI 50.19–60.61) (Table 2). Twenty-four patients (6.9%, 95% CI 4.24–9.56) experienced SD > 3 months but <6 months, and 132 patients (37.7%, 95% CI 32.62–42.78) had disease progression despite treatment.

In the Cox regression model, longer TTP was significantly associated with first-line treatment ($P = 0.037$) and

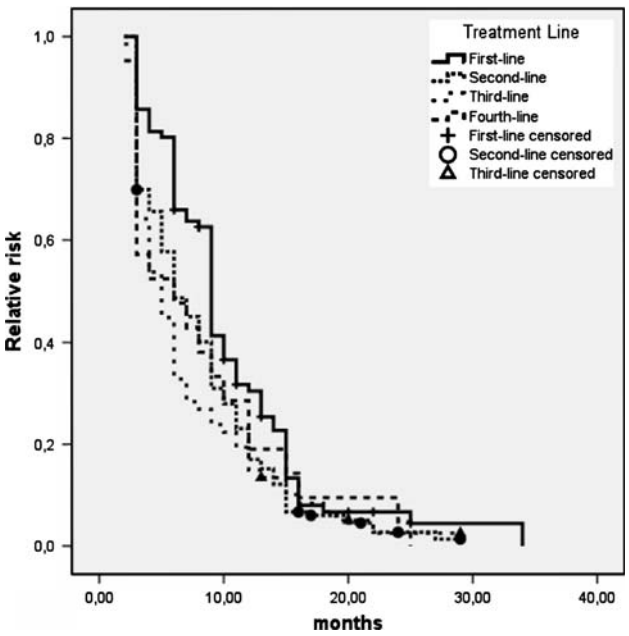



**Fig. 1** Time to progression (TTP) according to treatment line (months)

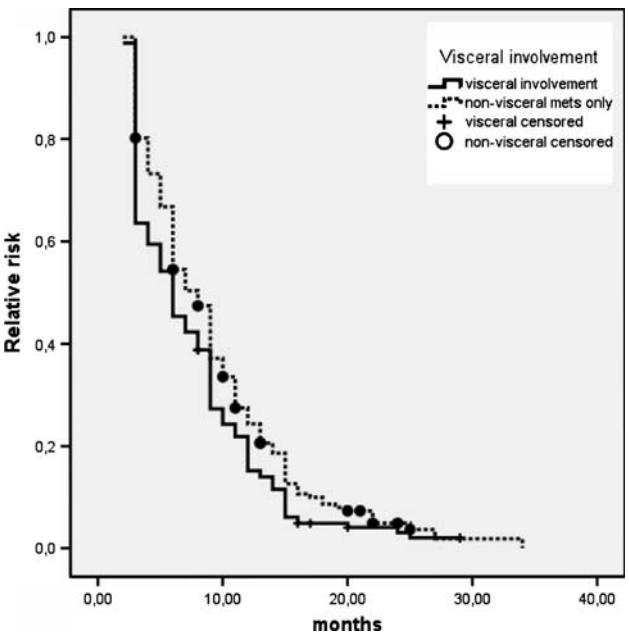



**Fig. 2** Time to progression (TTP) according to visceral involvement (months)

**Table 2** Response rates ($n = 350$)

| Number | | Response[a] | | | | | |
|---|---|---|---|---|---|---|---|
| | | CR | PR | SD ≥ 6 months | CBR | SD < 6 months | PD |
| Response overall | $n = 350$ | 8 (2.3%) | 43 (12.3%) | 143 (40.9%) | 194 (55.5%) | 24 (6.9%) | 132 (37.7%) |
| Response | | | | | | | |
| 1st line | $n = 92$ | 7 (7.6%) | 20 (21.7%) | 42 (45.7%) | 69 (75%) | 4 (4.3%) | 19 (20.7%) |
| 2nd line | $n = 170$ | 1 (0.6%) | 17 (10%) | 68 (40%) | 86 (50.6%) | 14 (8.2%) | 70 (41.2%) |
| Beyond 2nd line | $n = 88$ | – | 6 (6.8%) | 33 (37.5%) | 39 (44.3%) | 6 (6.8%) | 43 (48.9%) |

[a] CR, complete clinical response; PR, partial clinical response; SD ≥ 6 months, stable disease ≥6 months; SD > 3 < 6 months, stable disease <6 months; CBR, clinical benefit rate (CR + PR + SD ≥ 6 months); PD, progressive disease

**Table 3** Results—Cox regression Model

| Factor | Time to progression |
|---|---|
| Age | n.s. |
| PgR status | n.s. |
| Her2 status | n.s. |
| Time to disease recurrence <12 months | n.s. |
| Non-visceral disease only | $P = 0.007$ |
| Earlier palliative chemotherapy | n.s. |
| Fulvestrant as first-line hormonal therapy | $P = 0.037$ |

non-visceral disease only ($P = 0.007$). Other variables including age, Her2-status, PgR-status and prior palliative chemotherapy had no influence. Results from the multivariate analysis are summarized in Table 3.

### Tolerability

In this group of patients, many elderly and heavily pretreated, fulvestrant was well tolerated. A total number of 1,353 injections was administered. Main toxicities consisted of vasomotor symptoms (hot flashes), joint pain, nausea, and weight gain. One case of WHO grade 4 toxicity was reported; that patient experienced pulmonary embolism while on treatment. Grade 3 toxicities occurred in a total of eleven patients: five patients (1.4%) joint pain, five patients (1.4%) nausea and one patient (0.3%) hot flashes. Other toxicities (grade 1 and 2 only) consisted of headache, fatigue, weight gain, depression and thromboembolic events. Sixteen cases of mild local injection-site reactions were reported. All side effects are summarized in Table 4.

## Discussion

For the current report, data were analyzed from the Austrian Fulvestrant Registry that prospectively investigated the efficacy and tolerability of fulvestrant in postmenopausal women with metastatic breast cancer. Results demonstrate that fulvestrant 250 mg is an effective and well-tolerated hormonal treatment even in an elderly population. Time to progression was 7 months median; fulvestrant produced a response rate of 15% and further 41% had disease stabilization ≥6 months, resulting in a clinical benefit rate of 56%. Those data need to be discussed in the light of results from earlier clinical trials and other observational studies.

Two randomized phase III trials, Trial 0020 and Trial 0021, compared the efficacy and tolerability of fulvestrant 250 mg once monthly with anastrozole 1 mg daily in patients whose disease had progressed on prior endocrine treatment. In both trials, non-inferiority of fulvestrant was

**Table 4** Toxicity ($n = 350$)

| Toxicity | WHO grade | | | |
|---|---|---|---|---|
| | I | II | III | IV |
| Depression | – | 2 (0.6%) | – | – |
| Fatigue | 3 (0.9%) | 3 (0.9%) | – | – |
| Headache | 2 (0.6%) | – | – | – |
| Injection-site reactions | 16 (4.6%) | – | – | – |
| Joint pain | 45 (12.9%) | 31 (8.9%) | 5 (1.4%) | – |
| Nausea | 30 (8.6%) | 14 (4%) | 5 (1.4%) | – |
| Thromboembolic events | – | 1 (0.3%) | – | 1 (0.3%) |
| Vasomotor symptoms (hot flashes) | 49 (14%) | 17 (4.9%) | 1 (0.3%) | – |
| Weight gain | 3 (0.9%) | 2 (0.6%) | – | – |

demonstrated [21, 22]. A pre-planned combined analysis reported a median TTP of 5.5 months in the fulvestrant group; a response rate of 19.2% and clinical benefit rate of 43.5% was achieved [23]. A number of phase II studies reported similar observations: Steger et al. [25] published international results from the Fulvestrant Compassionate Use Programme. In a population of 339 postmenopausal patients, response rate was 11.8% and clinical benefit rate 39%. A trend was found towards better outcome in patients on first-line treatment. Other results are comparable: In a single centre study, fulvestrant produced a PR in nine of 111 patients and SD $\geq$ 6 months in another 38 patients, translating into a response rate of 8.1% and clinical benefit rate of 42.3%. The majority of patients received fulvestrant as beyond second-line treatment [24]. Mlineritsch et al. [26] in their patients found a RR of 8.3% and SD > 24 weeks in 29.6%, resulting in a clinical benefit rate of 28.9%. Median TTP was 6.4 months. Again, most patients received fulvestrant as third-, fourth-, or fifth-line hormonal treatment. Less favourable results were reported in the recently updated EFECT trial, which randomized patients to fulvestrant or exemestane upon progression on a non-steroidal AI. In both treatment arms, a median TTP of 3.7 months was observed. When analyzing those results it needs to be taken in account that 60% of those patients had received at least two earlier lines of endocrine therapy [27]. Similar efficacy data was reported in a Belgian study, where authors found a TTP of median 4 months [28]. Again, nearly have of patients had received two earlier lines of endocrine therapy.

With 7 months TTP and CBR 56%, our results appear somewhat superior. The majority of patients in the Fulvestrant Registry however received fulvestrant as first- or second-line therapy. When TTP curves from different treatment lines are compared, a significant difference becomes evident. Patients receiving fulvestrant as first-line therapy experienced TTP of median 9 months, while in second-line patients, TTP was 6 months and 5 months in third-line. This leads to the conclusion that fulvestrant is most effective when used early in the sequence of hormonal treatment. It is therefore important that treatment with fulvestrant does not preclude response to further endocrine therapy. In a retrospective subgroup analysis of patients treated within the above mentioned prospective phase III trials, 25/54 patients who derived CB on second-line fulvestrant achieved PR or SD $\geq$ 6 months on subsequent treatment with anastrozole, letrozole or megestrole acetate [29]. This is strengthened by data by Howell [30]. This group reported results from a trial in which fulvestrant was used as a first-line hormonal treatment. 20/35 patients experiencing CB with fulvestrant derived CB from subsequent endocrine therapy.

No significant difference in time to disease progression was observed between patients deriving clinical benefit from the last hormonal treatment-line before fulvestrant and those having SD < 6 months or PD. This result is strengthened by a recently published study conducted by Perey et al. [31]. This group compared clinical benefit rate and TTP between two patient groups on second-line fulvestrant treatment. Seventy were considered AI-responsive, and 20 had AI-resistant disease. No significant difference was found. Authors therefore concluded that response to AIs is not predictive for benefit with fulvestrant.

Presence of visceral metastases was significantly associated with shorter TTP in the Cox regression model. Patients with lung or liver metastases had earlier disease progression. Therefore, chemotherapy may be more advisable in patients with extensive or symptomatic visceral disease as outlined in current guidelines [32].

Her2-status and PgR-status, which might serve as surrogate for increased growth factor signalling in Her2-negative disease [17], had no significant influence on TTP in the multivariate model. This is an important difference to tamoxifen. In view of pre-clinical and clinical studies, tamoxifen resistance in Her2-positive disease was suggested [18, 33]. PgR negative disease also might be less responsive to selective oestrogen receptor modulators (SERMs) [33, 34]. This phenomenon is attributed to a bidirectional crosstalk between growth factor signalling pathways and ER [18, 35, 36], which confers that regulation of tumour growth is not under direct control of oestrogen [37].

Potential efficacy of fulvestrant in Her2-positive disease was reported in a single-centre study [19] as well as a retrospective analysis of Her2-positive patients treated at different centres [20]. Those results are now strengthened in this observation and may be explained by fulvestrant's mechanism of action. As it causes receptor down-regulation, it effectively blocks nuclear, cytoplasmatic and membrane-bound ER. The last two are usually held responsible for the above-mentioned crosstalk. Therefore it is hypothesised that fulvestrant, in difference to SERMs or AIs, might be able to effectively abrogate this interaction [16–18].

As reported in other trials, fulvestrant treatment was associated with low incidence of grade III/IV toxicity [23–26, 38]. One case of non-life threatening pulmonary embolism was observed, as well as a limited number of grade III joint pain, nausea, and hot flashes. Other toxicities consisted of depression, fatigue, weight gain, headache and mild injection-site reactions. In general, side effects were easily manageable and treatment was well tolerated. Of note is the relatively high proportion of patients >65 years in the study population. With 45%, this proportion is higher than what would usually be accrued to clinical trials, and is potentially more representative. Also in this specific subgroup, fulvestrant was effective and well tolerated.

In conclusion, fulvestrant appears to be an effective and well-tolerated treatment option in endocrine-responsive metastatic breast cancer. Similar to other hormonal treatment options, it is most effective when used in the first-line setting. Importantly, it is well tolerated also in the elderly. PgR- and Her2-status had no influence on time to progression, rendering it an attractive option in Her2-positive disease.

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