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CLINICAL TRIAL

Fulvestrant (Faslodex^{TM}) in advanced breast cancer: clinical experience from a Belgian cooperative study

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Abstract Fulvestrant (Faslodex^{TM}) is a new estrogen receptor (ER) antagonist with no agonist effects that is licensed for the treatment of postmenopausal women with hormone-sensitive advanced breast cancer (ABC) who have progressed/recurred on prior antiestrogen therapy. The Faslodex^{TM} Compassionate Use Program (CUP) provides expanded access to fulvestrant in countries where it is not yet available for patients who are not eligible to enter clinical trials. This analysis pools data from 402 patients who received fulvestrant as part of the CUP in Belgium, predominantly as 3rd- to 5th-line endocrine therapy for ABC. Two patients experienced partial responses and 118 experienced stable disease lasting ≥6 months, resulting in an overall clinical benefit rate of 29.9%. Fulvestrant was active in patients with multiple sites of metastases, visceral metastases, human epidermal growth factor receptor 2-positive disease and after heavy endocrine pre-treatment. Fulvestrant was well tolerated, with only six patients (1.5%) discontinuing treatment following adverse events. These data support the findings of previous CUP analyses and Phase II and III trials, suggesting that fulvestrant is a valuable addition to the treatment sequence for postmenopausal women with ABC who have progressed/recurred on prior endocrine therapy.

Keywords Advanced or metastatic breast cancer · Compassionate use · Endocrine · Fulvestrant · Postmenopausal

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Introduction

Fulvestrant (Faslodex^{TM}) is a novel estrogen receptor (ER) antagonist with no known agonist effects that binds, blocks and increases degradation of the ER Robertson et al. [1]. It is the first endocrine agent of this type to be licensed for the treatment of postmenopausal women with hormone-sensitive advanced breast cancer

(ABC) following progression/recurrence on prior antiestrogen therapy. This activity abrogates estrogen signaling through the ER Wakeling [2], Wakeling [3] and reduces the expression of estrogen-sensitive genes such as the progesterone receptor (PgR) Wakeling et al. [4].

This mechanism of action represents a treatment strategy that is distinct from partial antagonism of the ER with a selective ER modulator (SERM) such as tamoxifen or, in postmenopausal women, starving the ER of estrogen with an aromatase inhibitor (AI). Phase III trial data have shown fulvestrant to be at least as effective as the 3rd-generation AI anastrozole in the treatment of postmenopausal women with ABC who had progressed/recurred on prior antiestrogen therapy (predominantly with tamoxifen) Howell et al. [5], Osborne et al. [6]. In the combined analysis of data from these trials, neither time to progression (median 5.5 months and 4.1 months for fulvestrant and anastrozole, respectively), nor objective response (OR) rate (19.2% and 16.5% for fulvestrant and anastrozole, respectively) were significantly different between the two treatments Robertson et al. [7].

By extending the number of endocrine treatments available to women with ABC, it may be possible to delay the need for less well-tolerated cytotoxic chemotherapy, and thereby improve the quality of life for patients during their treatment. Endocrine therapies are usually given sequentially, with a new treatment prescribed following progression on the previous one. Over the past 30 years tamoxifen, and more recently the AIs, have dominated the endocrine treatment of both early breast cancer and ABC. Therefore, the majority of patients with ABC who have received previous hormonal therapy are likely to have experienced progression on one or both of these drugs and research continues to establish which the most effective therapy to give next is. However, the optimum endocrine treatment sequence may depend on individual patient or tumor characteristics and therefore may need to be tailored to each patient. The Faslodex™ Compassionate Use Program (CUP) allows access to fulvestrant where it is not commercially available for patients with ABC who have experienced progression on other endocrine therapies and who are not eligible for entry into clinical trials. CUPs necessarily have less stringent entry requirements than randomized clinical trials, but do offer the opportunity to collate data and experience of an agent in large groups of patients in real clinical situations.

Methods

Patients and assessments

Data were prospectively collected from centers participating in the CUP in Belgium. In this analysis, data from the 11 highest recruiting centers were pooled as follows: UZ Gasthuisberg (89 patients); AZ Sint Jan, Brugge (43 patients); St. Elisabeth, Turnhout (43 patients); Clinique St. Elisabeth, Namur (42 patients); Heilig Hartkliniek, Roeselaere (38 patients); AZ VUB, Jette (37 patients); AZ Middelheim, Antwerpen (36 patients); AZ Groeninge, Kortrijk (32 patients); UZ Gent (27 patients); Institut Jules Bordet, Brussels (eight patients); St. Augustinus, Wilrijk (seven patients).

All patients participating in the CUP were postmenopausal women with metastatic or recurrent ABC who had progressed following previous endocrine treatment with or without chemotherapy or radiotherapy. Informed consent was obtained from each patient.

ER and PgR tumor status of the primary tumor was assessed immunohistochemically, and some patients were also tested for overexpression of human epidermal growth factor receptor 2 (HER2). HER2 status was assessed using the Herceptest™ (Dako A/S, Glostrup, Denmark or other FDA-approved test kits), by dual color fluorescent in situ hybridization (FISH; PathVision™ HER2 DNA probe kit, Vysis Inc., Downers Grove, IL, USA). A score of +++ on the Herceptest was regarded as indicating a tumor to be HER2-positive. Tumors scoring ++ were subsequently tested using FISH to confirm HER2 status. Hormone receptor and HER2 status were classified as positive, negative or unknown (if no assessment had been made) for each receptor type. Data on demographics, disease history, treatment history and response to fulvestrant were collected for each patient from patient files or records.

Treatment and response to treatment

Fulvestrant was administered via intramuscular injection (250 mg every 28 days) until progression or other reason for discontinuation.

Response to treatment was assessed using either Response Evaluation Criteria in Solid Tumors (RECIST) criteria, or by the clinical judgment of the treating physician where the use of RECIST criteria could not be confirmed. Patients' response to treatment was assessed on a monthly basis for clinical benefit (CB). Complete response (CR) was classified as disappearance of all measurable lesions and no evidence of disease progression. Partial response (PR) was classified as a ≥30% decrease in the sum of the longest diameter of target lesions. Disease progression (PD) was classified as an increase of ≥20% in the sum of the longest diameter of target lesions, or the appearance of any new lesion. Stable disease (SD) was classified as neither sufficient shrinkage to qualify for a PR nor increase to qualify for PD lasting ≥6 months.

CB rate was defined as the sum of all patients experiencing CR, PR or SD ≥6 months. Due to variation in the

level of available detail for the history of certain patients, any patient receiving fulvestrant for ≥6 months was regarded as experiencing SD. Where dates of diagnoses and treatment for patients were recorded only as a year (or month/year), the first day of the year (or month) was considered to be the relevant date. This method was used to calculate only the time from diagnosis of EBC and ABC to receipt of fulvestrant; time on treatment was recorded separately and no estimations of these values were made. Time to progression (TTP) was measured from the date of the first dose of fulvestrant to the recorded date of PD. Adverse events were also recorded during fulvestrant treatment.

Results

Patients and baseline disease characteristics

This analysis includes 402 evaluable patients (401 females and one male), who received a total of 2212 injections of fulvestrant for ABC (mean 5.5 injections per patient). The median age of patients was 65 years (range 36–90 years; $n = 401$). No patients were still receiving fulvestrant at the time of this analysis.

Both ER and PgR status had been evaluated in 321 patients (79.9%; Table 1). More than half of the patient population (53.5%) had ER-positive/PgR-positive disease, and 18 patients (4.5%) were identified as having HER2-positive disease. The majority of patients (60.2%) had visceral metastases and nearly one third (30.6%) had metastases at ≥3 sites when treatment with fulvestrant was initiated (Table 1).

Overall, patients had a median time from first diagnosis of breast cancer to receiving fulvestrant of 101.5 months (range 9–444 months; $n = 400$), and a median time from diagnosis of advanced disease to receiving fulvestrant of 41 months (range 0–287 months; $n = 397$).

Table 1 Baseline disease characteristics

Characteristic	Number of patients	% of total patients ($n = 402$)
Hormone receptor profile		
ER-positive/PgR-positive	215	53.5
ER-positive/PgR-negative	73	18.2
ER-positive/PgR-unknown	11	2.7
ER-negative/any PgR	35	8.7
ER-unknown/PgR-unknown	68	16.9
HER2-positive	18	4.5
HER2-negative	204	50.7
HER2-unknown	180	44.8
Site of metastasis		
Bone only	91	22.6
Non-visceral	160	39.8
Visceral	242	60.2
<3 sites	279	69.4
≥3 sites	123	30.6

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

Previous breast cancer treatments

Endocrine and chemotherapeutic agents received by patients in the adjuvant setting and for advanced disease are shown in Table 2. Overall, patients received a median of three (range 0–14) therapies for advanced disease prior to fulvestrant; comprising a median of two endocrine therapies (range 0–6) and a median of one chemotherapy (range 0–10). Almost 80% of patients had received three or more endocrine therapies for ABC prior to fulvestrant.

Response to treatment

Overall clinical benefit rate and median time to progression

Of the 402 patients included in this analysis, two patients experienced PR and 118 experienced SD ≥6 months, giving an overall CB rate of 29.9%. Overall, median time to

Table 2 Previous therapies for breast cancer

Type of therapy	Number of patients	% of total patients ($n = 402$)
Adjuvant endocrine therapy only	109	27.0
Adjuvant chemotherapy only	59	14.6
Both adjuvant chemotherapy and endocrine treatment	106	26.4
No adjuvant treatment	127	31.6
Previous 3rd-generation AI for ABC	392	97.5
Previous tamoxifen for ABC	184	45.8
Both tamoxifen and 3rd-generation AI for ABC	181	45.0
Chemotherapy for ABC	206	51.2
No chemotherapy for ABC	196	48.8
Number of prior endocrine therapies for ABC		
1	3	0.7
2	80	20.0
3	139	34.6
4	116	28.9
5	54	13.4
6	9	2.2

progression with fulvestrant therapy was 4 months (range 1–33 months), and amongst patients with CB only (n = 120), median time to progression was 7 months (range 6–33 months).

Clinical benefit by hormone receptor status

CB rate was greater in patients with ER-positive/PgR-positive disease (CB rate 31.6%; n = 215), than in patients with ER-positive/PgR-negative disease (CB rate 21.9%; n = 73; Fig. 1). Six out of 18 patients with HER2-positive disease experienced CB (33.3%).

Clinical benefit rate by site of metastases

Sixty-three patients with visceral disease experienced CB with fulvestrant (CB rate 26.4%; n = 242), compared with 160 patients with non-visceral metastases (CB rate 35.0%; n = 160; Table 3). Notably, the CB rate achieved in patients with ≥3 sites of metastasis (CB rate 32.5%; n = 123) was similar to that in those with <3 sites of metastasis (CB rate 28.7%; n = 279; Fig. 2).

Clinical benefit rate by previous breast cancer therapy

CB rates of 25–35% were experienced by patients receiving fulvestrant as 2nd- to 5th-line endocrine therapy for ABC (Fig. 3a). The highest CB rate (33.8%) was experienced by patients who had received two prior endocrine therapies for ABC, although fulvestrant had clinically significant activity wherever it was used in the treatment sequence.

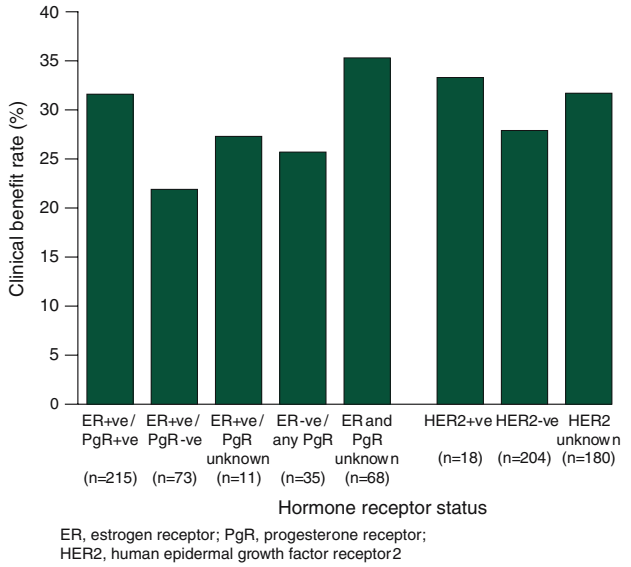

Fig. 1 Clinical benefit rate for patients treated with fulvestrant by hormone receptor and HER2 status

Table 3 Clinical benefit rate by type of metastases and previous cancer therapy

Patient group	n	PR, n	SD, n	CBR (%)
Type of metastases				
Bone only	91	1	27	30.8
Visceral metastases*	242	1	63	26.4
Non-visceral only	160	1	55	35.0
<3 sites of metastasis	279	1	79	28.7
≥3 sites of metastasis	123	1	39	32.5
Previous cancer therapies				
Adjuvant endocrine therapy only	109	0	31	28.4
Adjuvant chemotherapy only	59	1	19	33.9
Adjuvant endocrine and chemotherapy	105	0	25	23.8
No adjuvant therapy	129	1	43	34.1
Prior 3rd-generation AI for ABC	392	2	115	29.8
Prior tamoxifen for ABC	184	2	60	33.7
Both 3rd-generation AI and tamoxifen for ABC	181	2	57	32.6

PR; partial response; SD, stable disease ≥24 weeks; CBR, clinical benefit rate

*visceral metastases were those occurring in the lung, liver, stomach or intestines

A higher CB rate was achieved by patients who had not received any adjuvant therapy (CB rate 34.1%; n = 129) than in those who had received adjuvant endocrine treatment only (CB rate 28.4%; n = 109), or both adjuvant endocrine treatment and chemotherapy (CB rate 23.8%; n = 105; Fig. 3b and Table 3). The CB rate in patients who received adjuvant chemotherapy only was 33.9% (n = 59).

Amongst patients who received an AI immediately prior to fulvestrant (n = 193), the CB rate was 28.5% (one PR

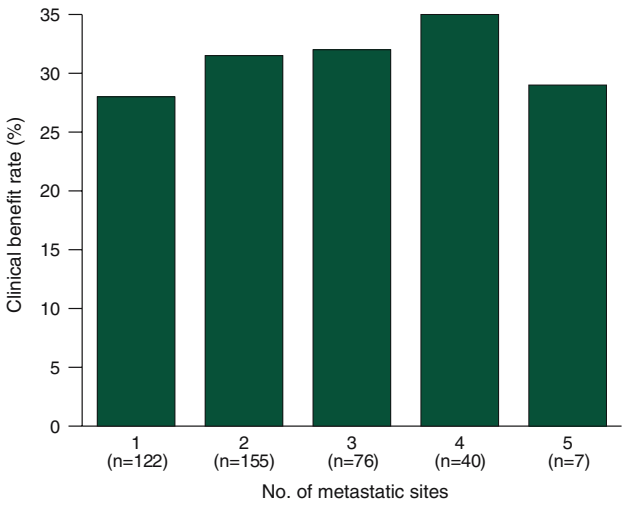

Fig. 2 Clinical benefit rate for patients treated with fulvestrant by number of metastatic sites

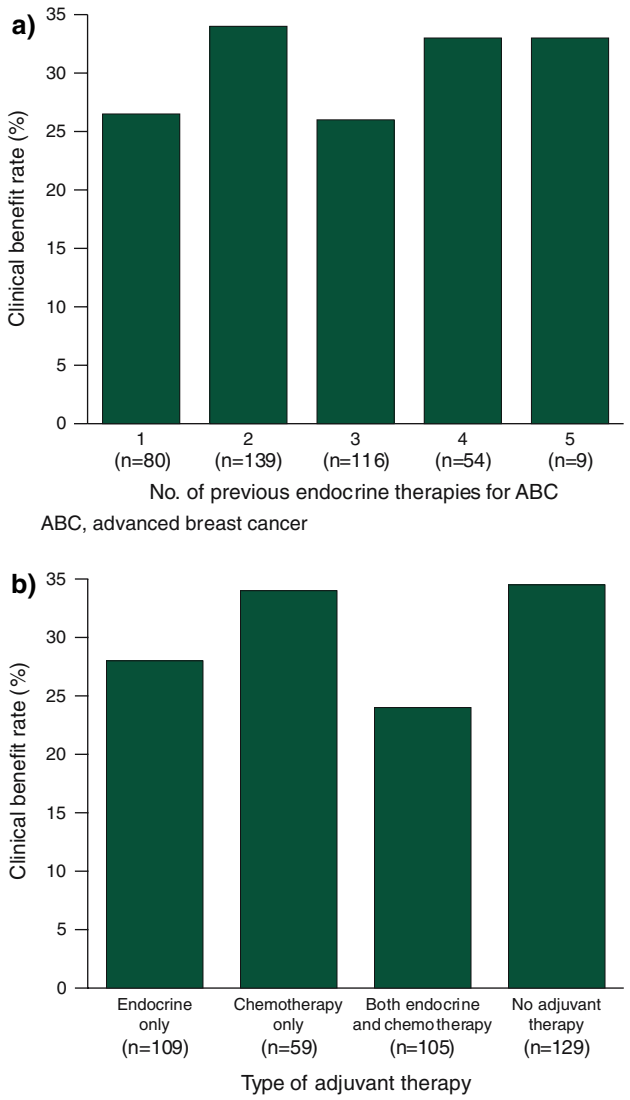

Fig. 3 Clinical benefit rate for patients treated with fulvestrant by (**a**) number of prior endocrine therapies for advanced disease (three patients received no prior endocrine treatment for ABC and one patient received six prior endocrine treatments [data not shown]) and (**b**) type of adjuvant therapy for early disease

and 54 SD ≥6 months). Amongst those who received chemotherapy immediately prior to fulvestrant (n = 169), the CB rate was 32.0% (one PR and 53 SD ≥6 months). Five patients received trastuzumab immediately prior to fulvestrant, of whom two experienced SD ≥6 months.

Combination therapy

Two patients achieved SD ≥6 months (8 months and 14 months), with a combination of fulvestrant and trastuzumab. Three other patients received fulvestrant combined with other agents. One patient progressed after 2 months' treatment with fulvestrant plus trastuzumab, after which a taxane was added to her therapy for a further 8 months. One patient had taxotere added to her treatment on progression after 3 months' fulvestrant (with a further 5 months before PD), and one patient had medroxyprogesterone acetate added to her treatment on progression after 4 months' fulvestrant (with a further 2 months before PD).

Adverse events

Six patients (1.5%) discontinued fulvestrant as a result of tolerability issues. Overall, at least one adverse event (AE) was recorded in 287 patients (71.4%), of which 15 patients experienced an AE considered to be related to fulvestrant. Of the patients experiencing treatment-related AEs, six patients reported pain on injection (four of which were moderate in severity), two had dyspnea, two had postprandial burden, two had musculoskeletal pain; and hot flashes, allergic reaction and general malaise each occurred in one patient.

Discussion

These data represent the largest single pool of clinical data from the Faslodex™ CUP to date. The majority of patients in this analysis had received considerable pre-treatment, with ~80% having progressed on two or more prior endocrine agents for ABC. Almost all patients had received a 3rd-generation AI at some point in their cancer therapy, and approximately half had received some form of chemotherapy. Fulvestrant was predominantly given as 3rd- to 5th-line endocrine therapy, i.e. quite late in their treatment history. The average time from first diagnosis to fulvestrant was ~8.5 years, and from diagnosis of ABC to fulvestrant was ~3.5 years.

Although these data are analyzed retrospectively, this type of analysis is valuable because it more closely reflects the activity of fulvestrant in a 'real-life' cohort of patients at varying stages in their ABC treatment.

The overall CB rate of ~30% demonstrates the activity of fulvestrant in a fairly heavily pre-treated patient population. This activity was present in patients with multiple sites of metastasis, patients with visceral metastases and in patients with HER2-positive disease, all patient groups who could be considered to be less responsive to endocrine therapy. The CB rate of ~30% did not appear to be affected by the treatment given immediately prior to fulvestrant, which was a 3rd-generation AI or chemotherapy in 90% of the population.

It was unexpected that no CRs and only two PRs were achieved in this pool of patients, although these patients were heavily pre-treated and could therefore be considered less responsive to endocrine therapy. However, this

observation may reflect the accuracy of response measurement across several treatment centers in a CUP, where reporting may not be as accurate as in randomized clinical trials.

Fulvestrant was well tolerated, with a low incidence of treatment-related AEs and injection-site reactions, which is in agreement with data from clinical trials Howell et al. [8], Robertson et al. [7]. However, it should be noted that AE reporting in CUPs is not as stringent as in the clinical trial setting, and that in a population of patients who are ill and have progressed on several previous therapies, it is often difficult to separate treatment-related AEs from events related to disease progression and worsening prognosis.

A previous analysis by Steger et al. of fulvestrant CUP data from a pool of 339 patients reported a CB rate of 39% in a patient population who had received a similar level of previous endocrine and chemotherapy Steger et al. [9]. It is interesting that although overall CB rate was higher in the Steger cohort, in both this dataset and the current CUP data there appears to be a more favorable CB rate in patients with ER-positive/PgR-positive tumors than those with ER-positive/PgR-negative disease. In both sets of data, fulvestrant displayed activity in patients with visceral metastases and in HER2-positive disease. Activity in patients with visceral metastases has also been reported in smaller cohorts of patients receiving fulvestrant via a CUP Cardoso et al. [10], Petruzelka et al. [11]**.** Such efficacy has also been reported in Phase III trials of fulvestrant versus anastrozole Mauriac et al. [12]**.**

In this analysis, fulvestrant demonstrated clinical activity following progression on an AI. Phase II data also demonstrate the activity of fulvestrant in postmenopausal patients who have experienced progression on an AI, with CB rates of 30–35% Ingle et al [13], Perey et al. [14]. These values compare with the CB rate reported from 60 patients receiving the steroidal AI exemestane following progression on both of the non-steroidal AIs anastrozole and letrozole (24.3–38.5%) Lønning et al. [15], Gennatas et al. [16]. Furthermore, first results from the Phase III Evaluation of Faslodex^{TM} vs. Exemestane Clinical Trial (EFECT) have recently been reported confirming the efficacy of fulvestrant in patients who have progressed/recurred on a non-steroidal AI (CB rates of 32.2% vs. 31.5% for fulvestrant and exemestane, respectively) Gradishar et al. [17].

As noted previously, the overall CB rate in this analysis was slightly lower than that seen in similar CUP analyses. Amongst this patient population, there were a number of patients ($n = 76$) who had their treatment discontinued after <3 months. Whilst some of these early discontinuations will have resulted from rapid PD, it is possible that some patients received insufficient treatment to experience a response; at a dose of 250 mg/month, fulvestrant is known to take 3–6 months to reach steady-state levels Robertson et al. [18]. The CB rate for the remaining 326 patients was 36.8%. It has been shown that time to response with fulvestrant is similar to that seen with anastrozole and tamoxifen in patients with ABC Robertson et al. [7], Howell et al. [8], Nabholtz et al. [19]. For each of these endocrine agents, median time to response fell in the range of 2.8–3.1 months. Therefore, it could be recommended that endocrine treatments for ABC should be evaluated after no less than 3 months' therapy, in the absence of rapid disease progression or tolerability problems.

These data support previous CUP and Phase II/III data showing CB with fulvestrant 250 mg/month in postmenopausal women with hormone-sensitive ABC following progression/recurrence on previous endocrine treatments. Activity of fulvestrant was retained in patients with visceral metastases, HER2-positive disease, and after considerable pre-treatment with other hormonal agents, showing the value of fulvestrant as an addition to the endocrine treatment sequence.

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