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Review

The therapeutic role of fulvestrant in the management of patients with hormone receptor-positive breast cancer

Eva Ciruelos [a,*], Tomás Pascual [a,1], María Luisa Arroyo Vozmediano [b,2], Marta Blanco [b,2], Luis Manso [a,1], Lucía Parrilla [a,1], Cesar Muñoz [a,1], Estela Vega [a,1], Monica Jackelin Calderón [a,1], Blanca Sancho [b,2], Hernán Cortes-Funes [a,1]

[a] Medical Oncology Department, Breast Cancer Unit, Hospital Universitario 12 de Octubre, Avda. de Córdoba s/n, 28041 Madrid, Spain
[b] Gynecology and Obstetrics Department, Breast Cancer Unit, Hospital Universitario 12 de Octubre, Avda. de Córdoba s/n, 28041 Madrid, Spain

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ABSTRACT

Although selective estrogen receptor modulators (SERMs), such as tamoxifen, or aromatase inhibitors (AIs), such as anastrozole, are the preferred endocrine treatment approach for most patients with hormone receptor-positive breast cancer, many patients progress despite this therapy or become resistant. Fulvestrant is a selective estrogen receptor down-regulator (SERD) that has demonstrated activity and efficacy in patients with hormone receptor-positive breast cancer previously untreated or treated with hormonal therapy. The efficacy of fulvestrant has been demonstrated in the neoadjuvant and metastatic settings, either alone or in combination with other therapies such as anastrozole or targeted drugs. Additionally, 500 mg of fulvestrant have been shown to be more effective than 250 mg, without significant differences in the toxicity profile. In this review, the unique mode of action of fulvestrant and the clinical data for different dosing regimens both alone or in combination with other drugs is critically assessed.

Introduction

Hormone receptor-positive breast cancer is the most common presentation of breast cancer today [1]. Several hormonal therapeutic options are currently available to treat postmenopausal women with this disease. The treatment options most extensively studied are selective estrogen receptor modulators (SERMs) and aromatase inhibitors (AIs), which constitute the standard therapeutic options for this setting. AIs are the standard of care in the first-line treatment of patients with breast cancer. Nonetheless, the SERM tamoxifen has also been widely used to treat both premenopausal and postmenopausal patients with advanced breast cancer as first-line treatment [2]. Eventually, patients develop tumor progression or resistance to tamoxifen. These patients are often treated with a second-line hormonal therapy [2]. Unfortunately, the vast majority of patients diagnosed with advanced breast cancer eventually progress or relapse during or after treatment with any of these specific therapies, and additional hormonal agents are needed to continue treating these patients at time of progression.

Fulvestrant is a estrogen receptor antagonist indicated for the treatment of postmenopausal women with estrogen receptor-positive, locally advanced or metastatic breast cancer for disease relapse on or after adjuvant antiestrogen therapy, or disease progression on therapy with antiestrogen [3]. Fulvestrant exerts selective estrogen receptor down-regulation (SERD), antiproliferative activity and induction of apoptosis. Additionally, it does not show cross-resistance with tamoxifen, or the estrogen receptor–agonist activity associated with tamoxifen [4]. Fulvestrant has been shown to be active in patients with breast cancer previously treated with a SERM such as tamoxifen, or with a non-steroidal AI such as anastrozole [5–7].

* Corresponding author. Tel.: +34 91 390 87 14; fax: +34 91 460 33 10.
E-mail addresses: eva.ciruelos@gmail.com (E. Ciruelos), tomaspascualmartinez@hotmail.com (T. Pascual), mlarroyov@yahoo.es (M.L. Arroyo Vozmediano), whitepontevedra@hotmail.com (M. Blanco), luis_manso@hotmail.com (L. Manso), luciaprubio@hotmail.com (L. Parrilla), burpee@hotmail.com (C. Muñoz), estela_1983@hotmail.com (E. Vega), mjca46@hotmail.com (M.J. Calderón), bsancho.hdoc@salud.madrid.org (B. Sancho), hcortes_funes@oncocenter.com (H. Cortes-Funes).
[1] Tel.: +34 91 390 87 14; fax: +34 91 460 33 10.
[2] Tel.: +34 91 390 80 00; fax: +34 91 460 33 10.

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This review describes the mechanism of action and resistance, as well as the therapeutic role of fulvestrant in the management of patients with hormone receptor-positive breast cancer. The efficacy and safety profiles of this drug are discussed using data from the most recent clinical trials of fulvestrant, alone or in combination, and at doses of 250 and 500 mg.

Mechanism of action and resistance of SERDs

SERDs are antiestrogens that have the main characteristic of being pure receptor antagonists. Fulvestrant is a SERD that competitively binds to estrogen receptors, with a binding affinity approximately 100 times greater than that of tamoxifen [4]. In animal models, this binding markedly attenuates the ability of the estrogen receptor to activate or inhibit gene transcription [8]. The mechanisms that underlie this binding include impaired dimerization, increased estrogen receptor turnover, and disrupted nuclear localization [9–11]. However, in contrast to tamoxifen, binding of fulvestrant to the estrogen receptor induces a rapid degradation and loss of the estrogen receptor protein in breast carcinoma cells, making the receptor unavailable or unresponsive to estrogen or estrogen agonists [12]. Fulvestrant works in a dose-dependent manner as indicated by the dose-related reduction of the estrogen receptor index [13]. Another characteristic that distinguishes the mode of action of fulvestrant from other antiestrogens currently in clinical use is that fulvestrant consistently reduces progesterone receptor levels in the tumor, also in a dose-dependent manner. Such a feature makes fulvestrant the first in a new class of antiestrogens and SERDs, without any agonist activity [4,14].

After prolonged therapy with fulvestrant, resistance is eventually acquired in the majority of patients with advanced breast cancer due to mechanisms that are poorly understood. One of the most discussed possibilities is the over-expression of the micro-RNAs miR-221/222. This over-expression in estrogen receptor-positive cell lines was shown to counteract the effect of estradiol depletion or of fulvestrant-induced cell death, conferring hormone-independent growth and fulvestrant resistance [15]. Fig. 1 shows the mode of action of estradiol and fulvestrant.

Efficacy of fulvestrant in patients with breast cancer

Several preclinical studies have demonstrated that fulvestrant was markedly more effective than tamoxifen in inhibiting the *in vitro* growth of human breast carcinoma cells and was also effective in tamoxifen-resistant breast carcinoma xenographs in *in vivo* mouse models [16,17]. Later on, a phase I trial demonstrated that a short-acting daily formulation of fulvestrant before primary breast surgery was well tolerated and had antiproliferative and antiestrogenic effects [18]. Subsequently, several phase II trials showed the activity of fulvestrant in breast cancer patients previously treated with tamoxifen and AIs [5,6,19,20]. While clinical studies have demonstrated a dose–response effect in the dose range of 50–250 mg of fulvestrant for intramuscular use [13], other trials testing the clinical activity of fulvestrant 125 mg did not show any objective tumor response after 3 months of treatment [21,22]. Therefore, subsequent clinical development of fulvestrant in advanced breast cancer was carried out with monthly dosages of 250 mg, although 500 mg have been later tested and compared with 250 mg.

Efficacy of fulvestrant 250 mg

Fulvestrant in comparison with anastrozole

Anastrozole is a highly selective third-generation AI that has been shown to be modestly superior to tamoxifen in the first-line treatment of advanced breast cancer [23], and to have a statistically significant survival advantage compared with megestrol acetate as a second-line treatment [24]. Also, the use of anastrozole in the adjuvant setting is now increasing after the results of the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial [25]. The clinical trial program of fulvestrant at 250 mg incorporated two multicenter, randomized phase III trials comparing fulvestrant with anastrozole. One of the trials, Trial 0020, was conducted in Europe, Australia and South Africa, while the other, Trial 0021, was conducted in North America [21,22]. Each trial compared a once-monthly intramuscular injection of fulvestrant (250 mg) with a once-daily oral dose of anastrozole (1 mg) in 851 postmenopausal women with advanced breast carcinoma who previously had disease progression after receiving endocrine treatment. The majority of patients included had received, and progressed on, tamoxifen.

Trials were prospectively designed to allow analysis of combined data [26]. The median TTP was 5.5 months in the fulvestrant arm and 4.1 months in the anastrozole arm (hazard ratio [HR]: 0.95; 95% CI: 0.82–1.10; $p = 0.48$), and the overall response rate (ORR) were 19.2% and 16.5% for fulvestrant and anastrozole, respectively (95% CI: 2.27–9.05; $p = 0.31$). Although the difference between treatments was not statistically significant, the results satisfied the criteria for demonstrating non-inferiority of fulvestrant compared with anastrozole. CBR were 43.5% and 40.9% in fulvestrant and anastrozole arms, respectively (95% CI: 4.42–9.36; $p = 0.51$). The

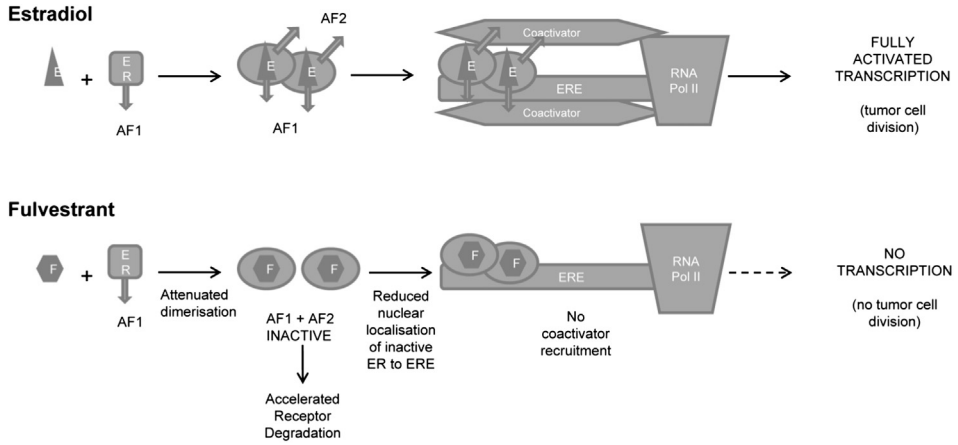

Fig. 1. Mode of action of estradiol and fulvestrant. AF1: activation function 1; AF2: activation function 2; E: estradiol; ER: estrogen receptor; ERE: estrogen response element; F: fulvestrant; RNA Pol II: ribonucleic acid polymerase II.

median duration of response from randomization to disease progression in responding patients was 16.7 months in the fulvestrant group and 13.7 months in the anastrozole group. In the ITT population, fulvestrant achieved a significantly longer median duration of response than anastrozole (HR: 1.30; 95% CI: 1.13–1.50; $p < 0.01$). At an extended median follow-up of 27 months, the median overall survival (OS) was similar between both treatment arms, being 27.4 months compared with 27.7 months in the fulvestrant- and the anastrozole-treated patients, respectively (HR: 0.98; 95% CI: 0.84–1.15; $p = 0.809$) [27]. Based on these results, fulvestrant 250 mg was registered as an additional option for postmenopausal patients with hormone-sensitive advanced breast cancer that have progressed on prior endocrine therapy.

Fulvestrant in comparison with tamoxifen

Howell et al. reported the first randomized trial comparing the efficacy and tolerability of fulvestrant with tamoxifen as the initial hormonal treatment of advanced breast cancer in postmenopausal women [28]. In this multicenter, double-blind, randomized trial, 587 patients with metastatic or locally advanced breast cancer previously untreated for advanced disease were randomly assigned to receive either fulvestrant (250 mg) by a monthly intramuscular injection or tamoxifen (20 mg) orally, once daily. At a median follow-up of 14.5 months, there was no significant difference between fulvestrant and tamoxifen in terms of median TTP (6.8 months and 8.3 months, respectively; HR: 1.18; 95% CI: 0.98–1.44; $p = 0.088$). In the subset of patients with estrogen receptor-positive and/or progesterone receptor-positive tumors (about 78% of patients), median TTP was 8.2 months for fulvestrant and 8.3 months for tamoxifen (HR: 1.10; 95% CI: 0.89–1.36; $p = 0.39$). The ORR for the overall population was 31.6% for fulvestrant and 33.9% for tamoxifen (odds ratio [OR]: 0.87; 95% CI: 0.61–1.24; $p = 0.45$), and 33.2% and 31.1% (OR: 1.10; 95% CI: 0.74–1.63; $p = 0.64$), respectively, in the hormone receptor-positive subgroup.

The CBR was 54.3% for fulvestrant and 62.0% for tamoxifen for the overall population ($p = 0.026$), with no significant differences in the subgroup of hormone receptor-positive patients (OR: 0.79; 95% CI: 15.01–3.19; $p = 0.22$). Estimated median OS was 36.9 months in the fulvestrant group and 38.7 months in the tamoxifen group (HR: 1.29; 95% CI: 1.01–1.64; $p = 0.04$) for the overall population, and 39.3 months compared with 40.7 months (HR: 1.16; 95% CI: 0.88–1.54; $p = 0.30$) in the hormone receptor-positive subset of patients, respectively. It was unexpected that fulvestrant showed neither superiority nor inferiority to tamoxifen in terms of TTP, but also that CBR and OS were significantly in favor of tamoxifen. In spite of this, it is important to point out that results were similar in both groups in the subset of patients with hormone receptor-positive disease.

Fulvestrant in comparison with exemestane

The third-generation non-steroidal AIs are increasingly used as adjuvant and first-line advanced therapy for postmenopausal patients with hormone receptor-positive breast cancer. Due to the fact that many patients subsequently develop disease progression or relapse, the identification of agents with efficacy after AI failure is a key aspect in this setting. Taking into account the prevalence of patients exposed to non-steroidal AI, the Evaluation of Faslodex versus Exemestane Clinical Trial (EFECT) was undertaken to determine the optimal hormonal agent to be administered after progression on non-steroidal AI [7]. EFECT was a randomized, double-blind, placebo-controlled, multicenter phase III study, in which a total of 693 postmenopausal women with hormone receptor-positive advanced breast cancer progressing or recurring after non-steroidal AI were randomized to receive exemestane (25 mg, orally once daily) or fulvestrant (500 mg intramuscularly on day 0; 250 mg on days 14 and 28; and 250 mg every 28 days thereafter).

Median TTP was 3.7 months in both groups (HR: 0.96; 95% CI; 0.82–1.13; $p = 0.653$); whereas ORR was 7.4% and 6.7% in the fulvestrant and exemestane arms (OR: 1.12; 95% CI: 0.58–2.19; $p = 0.736$), respectively; and CBR was 32.2% and 31.5% (OR: 1.03; 95% CI: 0.72–1.49; $p = 0.853$), respectively. The median duration of response, as measured from the date of random assignment, was 13.5 months in the fulvestrant arm and 9.8 months in the exemestane arm. The authors concluded that both drugs have similar activity in a significant proportion of postmenopausal women with hormone receptor-positive advanced breast cancer after progression on a non-steroidal AI [29].

Fulvestrant plus anastrozole in comparison with anastrozole

Some questions still remain unanswered regarding the optimal use of fulvestrant in the treatment of breast cancer, as the role of the combination of fulvestrant with an AI. Fulvestrant may be more effective in a low-estrogen environment, and this is supported by preclinical data [30,31]. The combination of letrozole plus fulvestrant was shown to be more effective in suppressing tumor growth than either letrozole or anastrozole or fulvestrant alone. Subsequently, two randomized trials have demonstrated the efficacy of the combination of fulvestrant and anastrozole as first-line treatment for patients with metastatic breast cancer [32,33]. In the open-label, prospective, randomized and phase III Fulvestrant and Anastrozole Combination Therapy (FACT) trial, a total of 514 postmenopausal women, or premenopausal women treated with gonadotropin-releasing hormone agonist, with advanced hormone receptor-positive breast cancer, were randomly assigned to receive fulvestrant (500 mg on day 1, and 250 mg on days 15, 29 and thereafter every 4 weeks) in combination with anastrozole (1 mg per day) or anastrozole alone at the same dosage [32]. It was observed that all efficacy outcomes evaluated such as TTP, ORR, CBR, duration of response and OS were similar between both treatment arms. In a similarly designed randomized, phase III trial performed by the Southwest Oncology Group (SWOG), 707 postmenopausal women with hormone receptor-positive metastatic breast cancer, without prior chemotherapy or immunotherapy for metastatic disease, were randomized to fulvestrant plus anastrozole or anastrozole alone at the same doses as the FACT trial [33].

Overall, median progression-free survival (PFS) was 15.0 months and 13.5 months in the combination and the anastrozole arms (HR for progression or death with the combination therapy: 0.80; 95% CI: 0.68–0.94; $p = 0.007$ by the log-rank test), respectively. Differences were even higher (no prespecified analyses) in 414 patients (59.7%) who did not receive prior tamoxifen therapy (17.0 months vs. 12.6 months, respectively; HR for progression or death with the combination therapy: 0.74; 95% CI: 0.59–0.92; $p = 0.006$ by the log-rank test), whereas it did not achieve statistical significance among 280 women (40.3%) previously treated with tamoxifen (13.5 months vs. 14.1 months, respectively; HR: 0.89; 95% CI: 0.69–1.15; $p = 0.37$ by the log-rank test). OS was also longer in patients treated with the combination than in those who received anastrozole alone (47.7 months vs. 41.3 months, respectively; HR for death: 0.81; 95% CI: 0.65–1.00; $p = 0.05$ by the log-rank test), despite the fact that 41% of patients in the anastrozole arm crossed over to fulvestrant after progression. Differences between trials could explain the discrepancy in results. In the SWOG trial 40% of patients had prior exposure to adjuvant tamoxifen, whereas this percentage rose to 70% in the FACT trial. Moreover, in the SWOG trial when patients were stratified according to prior tamoxifen exposure, only patients without previous tamoxifen showed statistically significant differences in terms of PFS.

Fulvestrant 250 mg vs. fulvestrant 500 mg

One of the approaches to optimizing the use of fulvestrant in breast cancer is the investigation of higher doses.

Previous rationale

A multicenter, randomized and partially blinded study compared the effects of different doses of fulvestrant with tamoxifen or placebo on estrogen receptor and progesterone receptor levels, Ki-67 proliferation-associated antigen labeling index (Ki-67LI), and the apoptotic index in the primary breast tumors of postmenopausal women [13]. A total of 201 women with primary breast cancer were randomized to receive a single intramuscular dose of fulvestrant (either of 50 mg, 125 mg or 250 mg), oral tamoxifen (20 mg daily) or matching tamoxifen placebo for 14–21 days before tumor resection surgery with curative intent. Fulvestrant produced dose-dependent reductions in estrogen receptor and progesterone receptor H-scores as well as in the Ki-67LI. The reduction of estrogen receptor expression was significantly higher with all doses of fulvestrant when compared with placebo (50 mg, $p = 0.026$; 125 mg, $p = 0.006$; 250 mg, $p = 0.0001$), and with fulvestrant 250 mg when compared with tamoxifen ($p = 0.024$). However, the reduction of progesterone receptor was only significant with fulvestrant 125 mg ($p = 0.003$) and 250 mg ($p = 0.0002$) compared with placebo.

Additionally, all doses of fulvestrant significantly reduced Ki-67LI compared with placebo (50 mg, $p = 0.046$; 125 mg, $p = 0.001$; 250 mg, $p = 0.0002$), but there were no significant differences in this variable between any doses of fulvestrant and tamoxifen. Finally, fulvestrant did not alter the apoptotic index when compared with either placebo or tamoxifen ($p = 0.238$). These results showed that fulvestrant produced a marked dose-dependent reduction in estrogen and progesterone receptor expression, and Ki-67LI. However, it is important to consider that these results may have been influenced by a less-than-optimal exposure of both fulvestrant and tamoxifen during the study, as the time to steady-state for tamoxifen is about 4 weeks and that for fulvestrant is 3–6 months [3,34].

Neoadjuvant setting

The Neoadjuvant Endocrine Therapy for Women with Estrogen-Sensitive Tumors (NEWEST), open-label, randomized phase II study compared fulvestrant at 500 mg with 250 mg as neoadjuvant endocrine therapy in terms of biological activity (expression of estrogen and progesterone receptors, and Ki-67LI), ORR and tolerability in postmenopausal patients with locally advanced breast cancer [35]. A total of 211 women were allocated to receive 500 mg (plus 500 mg on day 14 of the first month) vs. 250 mg per month of fulvestrant for 16 weeks before surgery. At week 4, according to H score, the dose of 500 mg resulted in a greater reduction of estrogen and progesterone receptor as well as in Ki-67LI compared with the dose of 250 mg ($p < 0.0001$, $p = 0.0018$, $p < 0.0001$, respectively). Although the results of this study may provide evidence of greater biological activity for the 500 mg dose of fulvestrant, differences may be also attributable to the loading element of fulvestrant undertaken in the fulvestrant 500 mg arm, as the steady-state in this treatment arm was reached at 4 weeks.

Efficacy of fulvestrant 500 mg in the metastatic setting

After neoadjuvant data of the efficacy of Fulvestrant 500 mg, different studies were designed in the metastatic setting [13,35,36].

FIRST trial

The Fulvestrant First-Line Study Comparing Endocrine Treatment (FIRST) was a multicenter, open-label, randomized, phase II trial that compared the efficacy of fulvestrant 500 mg with anastrozole in the first-line setting [37,38]. In total, 205 postmenopausal patients with hormone receptor-positive locally advanced or metastatic breast cancer who were not amenable to therapy of curative intent were randomly assigned to receive 500 mg of fulvestrant monthly plus 500 mg on day 14 of the first month or 1 mg/day of anastrozole. The primary endpoint was CBR defined as the proportion of patients experiencing an objective response or stable disease for at least 24 weeks.

Although there were no significant differences between fulvestrant and anastrozole in terms of CBR and ORR ($p = 0.386$ for CBR and $p = 0.947$ for ORR), the observed CBR confirmed the high clinical efficacy of both agents. In contrast, median TTP was significantly longer with fulvestrant than with anastrozole (23.4 months vs. 13.1 months, respectively; HR: 0.66; 95% CI: 0.47–0.92; $p = 0.01$), corresponding to a 34% reduction in the risk of progression. Kaplan–Meier curves for TTP indicate that fulvestrant 500 mg may be of benefit for early progressive patients. This treatment effect was consistent across all pre-defined subgroups. Also, reflecting the TTP advantage of fulvestrant over anastrozole, duration of response, duration of clinical benefit and time to treatment failure (TTF) favored fulvestrant. Median TTF was 17.6 months with fulvestrant and 12.7 months with anastrozole (HR: 0.73; 95% CI: 0.54–1.00; $p = 0.05$). This trial shows that another endocrine agent may be more effective than an AI in this setting. Taking into account that these results are from a randomized phase II open-label trial, a phase III registration trial needs to be performed to confirm the role of fulvestrant 500 mg in this setting.

CONFIRM trial

Results of prior research led to the design of the Comparison of Faslodex in Recurrent or Metastatic Breast Cancer (CONFIRM) study, a multicenter, double-blind, phase III trial that included 736 postmenopausal patients with locally advanced or recurrent estrogen receptor-positive breast cancer who experienced progression after prior endocrine therapy with tamoxifen or AIs [36,39]. Patients were randomized to receive 500 mg of fulvestrant (500 mg on day 0, 14, 28, and every 28 days thereafter) or 250 mg of fulvestrant every 28 days. Results showed that the 500 mg regimen of fulvestrant was associated with a significantly longer PFS than the 250 mg regimen (6.5 months vs. 5.5 months, respectively; HR: 0.80; 95% CI: 0.68–0.94; $p = 0.006$); however, similar results were obtained in terms of ORR ($p = 0.795$) and CBR ($p = 0.100$). In a longer not pre-planned follow-up analyses [39], median OS was significantly longer with 500 mg of fulvestrant than with 250 mg (26.4 months vs. 22.3 months; HR: 0.81; 95% CI: 0.69–0.96; $p = 0.016$). The benefit in terms of OS demonstrated by fulvestrant in the CONFIRM trial is a key aspect in this setting, because very few drugs have demonstrated improvements in OS in patients with metastatic breast cancer. From the publication of the results of this trial, Fulvestrant at 500 mg has become the preferred schedule for this drug.

Efficacy of fulvestrant 250 mg and 500 mg in the metastatic setting

Martín et al. [40], designed the randomized, open label, phase III LEA trial to address the hypothesis that anti-vascular endothelial growth factor (anti-VEGF) treatment can prevent resistance to hormone therapy in patients with endocrine responsive advanced breast cancer. This trial assessed the combination of bevacizumab with letrozole or fulvestrant (250 mg) as first-line therapy in 380 patients with these characteristics. This study failed to demonstrate

a statistically significant increase in terms of PFS for the combination of endocrine therapy and bevacizumab in comparison with endocrine therapy alone. In addition, the combination did not demonstrate an impact on OS either.

Safety of fulvestrant 250 mg and 500 mg in advanced breast cancer

In the European and American trials (Trial 0020 and Trial 0021) that compared fulvestrant 250 mg with anastrozole, both treatments were well tolerated, with a similar incidence of adverse events [21,22,26]. The only significant difference observed was the incidence of joint disorders, including arthralgia, arthrosis and arthritis, which occurred more frequently in patients receiving anastrozole ($p = 0.0234$) (Table 1). The most common adverse events in both treatment groups, were nausea (26.0% vs. 25.3%), asthenia (22.7% vs. 27.0%), pain (18.9% vs. 20.3%), vasodilation (17.7% vs. 17.3%), and headache (15.4% vs. 16.8%) for the fulvestrant group and the anastrozole group, respectively. Withdrawals due to drug-related adverse events were 0.9% and 1.2% in the fulvestrant arm and the anastrozole arm, respectively. The CONFIRM trial showed that both doses of fulvestrant (250 mg and 500 mg) were well tolerated with no substantial differences in the incidence and severity of prespecified adverse events (Table 1). Also, the quality of life between arms was similar with both dosages [36]. Serious adverse events reported in more than 2 patients were bronchitis, dyspnea, and vomiting in the 500 mg group, and there were no cases reported in the 250 mg group.

Data from the FIRST trial showed that fulvestrant 500 mg was well tolerated with an adverse events profile comparable to that of anastrozole and consistent with that previously reported in the CONFIRM trial and NEWEST trials [35–37]. The incidence of serious adverse events was 11.9% with fulvestrant 500 mg and 9.7% with anastrozole. There were no significant differences between treatments in the incidence of any of the prespecified adverse events (Table 1). The most common adverse events in the fulvestrant 500 mg arm were bone pain (13.9%), nausea (10.9%), arthralgia (9.9%), constipation (9.9%), vomiting (8.9%) and dyspnea (8.9%). In the anastrozole arm, the most common adverse events were hot flashes (13.6%), headache (12.6%), bone pain (9.7%), arthralgia (8.7%) and myalgia (8.7%). The incidence of arthralgia was similar between the two arms, but headache and asthenia were less frequent in the fulvestrant arm [37].

Other mentioned trials showed no differences in terms of safety data of fulvestrant in comparison with the control drugs, such as the EFECT and the FACT trials [7,32]. Only the FACT trial showed a higher incidence of hot flashes in the combination arm compared with the single treatment arm ($p = 0.003$) [32]. In general, fulvestrant is well tolerated, with no significant toxicities and very low frequency of treatment dropout. This is essential in the treatment of advanced breast cancer, where treatment tolerance and quality of life should be important factors in treatment decisions. In addition, there were no significant differences between the toxicity profiles of fulvestrant and other hormonal therapies such as anastrozole, tamoxifen and exemestane, or between both doses of fulvestrant in the treatment of hormone-sensitive advanced breast cancer.

Ongoing research with fulvestrant in breast cancer

As described previously, patients with estrogen receptor-positive breast cancer benefit from AI as first-line therapy, but many of them develop resistance to these drugs due to the upregulation of signaling pathways such as phosphoinositide-3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) and human epidermal growth factor receptor type 2 (HER2)/mitogen-activated protein kinase (MAPK) [41–43].

Fulvestrant in combination with mTOR-PI3KCA inhibitors

Preclinical studies had demonstrated that the sensitivity to hormonal therapy may be restored by treatment with mTOR inhibitors such as everolimus [44]. Subsequently, a randomized phase II trial showed that everolimus significantly increased letrozole efficacy in the neoadjuvant setting in patients with estrogen receptor-positive breast cancer [45]. Also, a randomized phase III trial showed that everolimus in combination with an AI such as exemestane improved PFS over exemestane alone (6.9 months vs. 2.8 months; $p < 0.001$) in women with hormone receptor-positive advanced breast cancer previously treated with non-steroidal AI [46]. The combination of everolimus with tamoxifen also increased CBR, TTP and OS compared with tamoxifen alone in postmenopausal women with hormone receptor-positive, HER2-negative and AI resistant metastatic breast cancer [47].

According to these results and taking into account that fulvestrant is one standard option for second-line hormonal treatment, several ongoing trials are testing the combination of fulvestrant with PI3K inhibitors, such as BYL719, GDC-0941, GDC-0980 and BKM120. BYL719 is an oral PI3K inhibitor that strongly and selectively inhibits the PI3Kα isoform of PI3K and shows statistically significant dose-dependent anti-tumor efficacy in *PIK3CA* mutant xenograft models in rodents [48]. In an ongoing phase I trial, BYL719 as single agent or in combination with fulvestrant is being administered to patients with estrogen receptor-positive *PIK3CA*-mutated advanced breast cancer progressed despite standard therapy or for whom no standard therapy exists (ClinicalTrials.gov identifier NCT01219699).

Table 1
Adverse events observed in patients treated with different endocrine therapies.

Adverse events	0020 and 0021 trials [27]		CONFIRM trial [36]		FIRST trial [37]	
	Fulvestrant 250 mg $N = 428$ *n* (%)	Anastrozole 1 mg $N = 423$ *n* (%)	Fulvestrant 250 mg $N = 374$ *n* (%)	Fulvestrant 500 mg $N = 361$ *n* (%)	Fulvestrant 500 mg $N = 101$ *n* (%)	Anastrozole 1 mg $N = 103$ *n* (%)
Gastrointestinal disturbances	206 (49)	192 (45)	76 (20)	73 (20)	28 (28)	23 (22)
Hot flashes	92 (22)	94 (22)	23 (6)	30 (8)	13 (13)	14 (14)
Injection site reactions	NR	NR	50 (13)	49 (14)	NR	NR
Ischemic cardiovascular disorders	NR	NR	7 (2)	5 (1)	0 (0)	1 (1)
Joint disorders	35 (8)[a]	54 (13)[a]	70 (19)	68 (19)	14 (14)	10 (10)
Thromboembolic events	15 (4)	19 (5)	0 (0)	3 (1)	0 (0)	0 (0)
Urinary tract infection	37 (9)	25 (6)	8 (2)	8 (2)	4 (4)	1 (1)
Vaginitis	11 (3)	8 (2)	1 (0.3)	3 (1)	0 (0)	0 (0)
Weight gain	6 (1)	9 (2)	1 (0.3)	1 (0.3)	1 (0)	0 (0)

[a] Only this adverse event is significantly different in both treatment arms ($p = 0.0234$). NR: not reported.

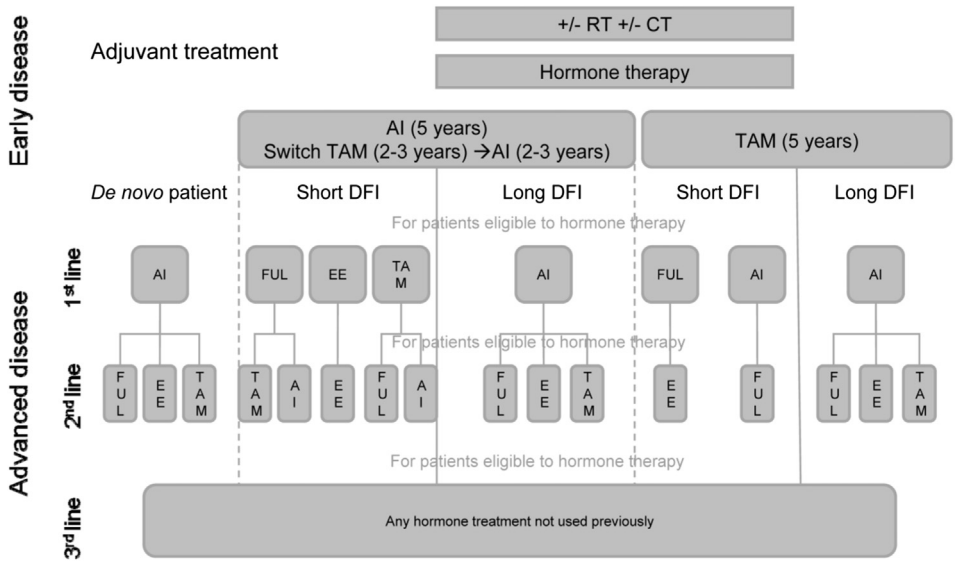

Fig. 2. Treatment algorithm for postmenopausal patients with hormone receptor-positive and HER2-negative breast cancer.* AI: aromatase inhibitor; CT: chemotherapy; DFI: disease-free interval; EE: exemestane plus everolimus; FUL: fulvestrant; HER2: human epidermal growth factor receptor type 2; HR: hormone receptor; RT: radiotherapy; TAM: tamoxifen. Short DFI: relapse occurs during adjuvant treatment administration or within the first 12 months after finishing it. Long DFI: relapse occurs after 12 months from the end of adjuvant hormonal treatment administration. *All treatment decisions should take into account the toxicity profile of different drugs and patient preferences.

The discovery of potent, selective class I PI3K and mTOR kinase inhibitors for the treatment of cancer has led to their clinical development for breast disease. Currently, a double-blind, placebo-controlled, randomized phase II trial is comparing two orally available PI3K and mTOR inhibitors, GDC-0941 and GDC-0980, in combination with fulvestrant, with fulvestrant alone in patients with advanced breast cancer who are resistant to AI therapy (ClinicalTrials.gov identifier NCT01437566). Preliminary results are expected at the end of 2015.

BKM120 is another potent and highly specific oral pan-class I PI3K inhibitor. Unlike other inhibitors, it does not inhibit the related mTOR and Vps34 kinases. Currently, two randomized phase III trials are evaluating the role of this drug in the treatment of patients with hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer. The BELLE-2 study is testing the combination of fulvestrant with or without BKM120 in patients refractory to AI (ClinicalTrials.gov identifier NCT01610284). The BELLE-3 study is evaluating the combination of fulvestrant with or without BKM120 in patients who have progressed on or after a mTOR inhibitor-based treatment (ClinicalTrials.gov identifier NCT01633060).

Fulvestrant in combination with EGFR inhibitors

Gefitinib is a selective inhibitor of the epidermal growth factor receptor (EGFR), this receptor is overexpressed in certain types of human carcinomas, such as lung and breast cancer. A phase II trial evaluating the efficacy of the combination of gefitinib 250 mg with fulvestrant 250 mg in advanced or metastatic breast cancer with estrogen receptor-positive and/or progesterone receptor-positive disease has been completed recently (ClinicalTrials.gov identifier NCT00234403).

Fulvestrant as first-line treatment

Lastly, the FALCON study, a multicenter, double-blind, randomized, phase III trial is currently ongoing to compare the efficacy in terms of PFS and tolerability of fulvestrant 500 mg with anastrozole 1 mg as endocrine treatment for postmenopausal women with hormone receptor-positive locally advanced or metastatic breast cancer who have not previously been treated with any hormonal therapy (Clinicaltrials.com identifier NCT01602380). This trial could change future recommendations of hormonal therapy in the first-line setting.

Fulvestrant for premenopausal patients

Fulvestrant has been studied little in premenopausal women despite of its attractive mechanism of action. Nonetheless, a randomized phase II trial is currently studying the combination of fulvestrant with goserelin an injectable gonadotropin-releasing hormone superagonist used for ovarian suppression in premenopausal women. In this trial, the activity of fulvestrant plus goserelin is compared with anastrozole plus goselerin and goselerin alone in premenopausal women with recurrent or metastatic estrogen receptor-positive breast cancer (ClinicalTrials.gov identifier NCT01266213).

The current therapeutic role of fulvestrant in breast cancer

AIs are the preferred treatment approach for most postmenopausal women with hormone receptor-positive advanced breast cancer, but many of these patients progress or become resistant to these drugs. Fulvestrant has been demonstrated to be active in patients with breast cancer previously treated with tamoxifen or non-steroidal AI. This benefit was seen in two phase III trials with fulvestrant at 250 mg (32.2–39.6%) and 500 mg (45.6%) in patients resistant to a previous AI [7,36]. Fulvestrant was also shown to be effective in breast cancer patients previously untreated with hormonal therapy (FIRST trial) with a higher clinical benefit than anastrozole [37,38]. The NEWEST trial demonstrated the efficacy of fulvestrant in the neoadjuvant setting at a dose of 500 mg [35]. Taking into account its different mechanism of action, fulvestrant may be administered with a LHRH agonist to premenopausal women with breast cancer. Several studies have evaluated fulvestrant in premenopausal women with breast cancer and compared results with placebo or tamoxifen [49], with an adequate safety and efficacy profile (TTP 5 months and CBR 45.5%). Fulvestrant has also shown a good and predictable safety profile in several

randomized trials [7,27,28,32,33], even at high doses (FIRST and CONFIRM trials) [37].

Another potential advantage of fulvestrant is that it may improve treatment compliance due its monthly parenteral administration compared with daily oral intakes of other endocrine therapies. Adherence of oral long-term treatments is a major problem that should be considered [50]. It is estimated that around 20% of breast cancer patients receiving oral endocrine therapy do not take their medication regularly, primarily in the adjuvant setting where benefit of treatment is not clearly perceived by patients [51]. Parenteral administration of fulvestrant provides greater control over endocrine treatment compliance, reducing oral absorption and pharmacokinetic interactions with food or other drugs, which are important aspects to be considered in patients with breast cancer who usually are receiving multiple medications. Lastly, fulvestrant may be effectively combined also with targeted drugs. Due to greater understanding of the molecular pathways involved in the development of cancer, several trials are evaluating the role of new biological drugs which block signaling pathways. New drugs such as the mTOR inhibitor everolimus, and the PI3K inhibitors such as BYL719, GDC-0941, GDC-0980, and BKM120, are being assessed in combination with fulvestrant for the treatment of breast cancer. Fig. 2 describes a treatment algorithm for postmenopausal patients with hormone receptor-positive and HER2-negative breast cancer.

Conclusions

Fulvestrant is a SERD that does not have the agonist activity seen with tamoxifen, so it can be administered in postmenopausal women with hormone receptor-positive advanced breast cancer who have disease progression on tamoxifen or AI. Research is also focused in premenopausal women, with optimal results so far. Fulvestrant has also been shown to be active in patients previously untreated with endocrine therapies, either in the neoadjuvant or in the metastatic setting, alone or in combination with other therapies such as AI or targeted drugs. Higher doses, i.e. 500 mg of fulvestrant, have proven to be more effective than the dose of 250 mg, without any significant difference in the toxicity profile. Taking all these factors together, fulvestrant is an alternative for patients with hormone-responsive advanced breast cancer who have progressed on other endocrine therapies and who need a well-tolerated alternative that improves treatment compliance.

Conflict of interest statement

The authors declare that they do not have any conflict of interest that may inappropriately influence this work.

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