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# Fulvestrant in hormonal treatment of breast cancer

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### ABSTRACT

Fulvestrant is a selective oestrogen receptor (ER) down-regulator (SERD), which lacks partial agonistic properties characteristic for selective oestrogen receptor modulators (SERM). The drug is indicated for the treatment of hormone receptor-positive metastatic breast cancer in postmenopausal women with disease progression following antioestrogen therapy. The initial recommendation of a 250-mg dose was based on the results of clinical trials, which revealed that fulvestrant was non-inferior to anastrozole in this indication. However, the higher the dose of fulvestrant, the more effective it is. The CONFIRM trial compared a 500-mg dose with the approved dose of fulvestrant of 250 mg per month for treatment of postmenopausal women with oestrogen receptor-positive advanced breast cancer, who progressed after prior endocrine therapy. It showed that the higher dose was associated with a statistically significant increase in progression-free survival without increased toxicity, and it became the basis of approval of a fulvestrant dose of 500 mg in 2010. The drug should be administered intramuscularly on days 0, 14 and 28 and once monthly thereafter. The phase III FALCON trial, to which postmenopausal breast cancer patients who had not received previous endocrine therapy were eligible, revealed that a 500-mg fulvestrant dose reduced the risk of progression by 20% compared with anastrozole in first-line treatment. Fulvestrant is also beneficial in third and further lines of hormonal treatment of breast cancer and remains efficacious in young patients treated with LHRH analogue. There have also been numerous trials investigating the efficacy of fulvestrant combined with molecular targeted therapy in patients with hormone-resistant metastatic breast cancers. This review summarises the mechanism of action of fulvestrant and the results of the most important clinical trials dedicated to this drug.

**Key words:** breast cancer, hormonal therapy, fulvestrant, hormone-resistance

Oncology in Clinical Practice  
 2017, Vol. 13, No. 1, 14–23  
 DOI: 10.5603/OCP.2017.0003  
 Translation:  
 dr n. med. Dariusz Stencel  
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 ISSN 2450–1654

Oncol Clin Pract 2017; 13, 1: 14–23

## Introduction

Breast cancer represents the first cause of cancer morbidity and the second cause of cancer-related deaths in Poland (National Cancer Registry). In 2013 there were over 17,000 newly diagnosed breast cancer patients. It is estimated, that in western countries approximately 80% of breast cancer is hormone-sensitive [1]. According to the data from the US SEER (Surveillance, Epidemiology, and End Results) database, approximately 6% of patients with newly diagnosed breast cancer have disseminated disease at diagnosis, and in the remaining patients the risk of recurrence as metastatic disease depends on baseline stage, cancer biology, and used treatment. In patients with hormone-sensitive, HER2 (human epidermal growth factor receptor 2)-negative breast cancer the

treatment of choice is hormone therapy, provided that the malignant process is not extremely aggressive and there is no threat of precipitate insufficiency of critical internal organs. The choice of hormone therapy pattern is based on the patient's menopausal status. Currently used drugs in this indication include luteinising hormone-releasing hormone analogue, LHRH analogue, selective oestrogen receptor modulators, SERM, e.g. tamoxifen, steroidal aromatase inhibitors, SAI, e.g. exemestane, and nonsteroidal aromatase inhibitors, NSAI, e.g. anastrozole, letrozole, and fulvestrant as selective oestrogen receptor (ER) down regulator (SERD) [1]. The emergence of fulvestrant at the beginning of 1990s in antineoplastic drugs armamentarium was the result of many years of research on anti-oestrogen deprived a partial agonistic activity, as drugs from SERM group

have [2]. The final compound was obtained by chemical modification of oestradiol in position  $7\alpha$ . Because the drug is sparsely absorbed from gastrointestinal tract, it is available in the form of a long-acting solution for intramuscular injections. In the presented article, we discuss the mechanism of action of fulvestrant and its worth in clinical practice based on data from the most important clinical trials.

### Comparison of SERM and fulvestrant mechanisms of action

Oestrogens impact the tissues through oestrogen receptors (ERs). After binding with a hormone, ERs split off heat shock proteins (HSPs), undergo dimerisation, and localise in the cellular nucleus. Then dimers are bound to DNA in regulatory regions of targeted genes, precisely in places called oestrogen response elements (EREs). Transcription of selected genes is regulated through two activating functions of oestrogen receptors: AF1 and AF2, which induce incorporation of the subsequent elements to transcription complex — coactivators or corepressors. These elements activate or inhibit polymerase II RNA activity. The receptor's fragment with AF1 activity (free amine group  $-NH_2$  located at the end of a polypeptide) is regulated by growth factors engaged in mitogen-activated protein kinase (MAP kinase) pathway, while activity of ligand-binding fragments AF2 (polypeptide end  $COOH$ ) depends on oestradiol. Full agonistic receptor function is possible due to coexistence of both activities. Mechanisms of action (MoA) of tamoxifen and its metabolites and oestrogens are comparable, and the difference is based on deactivated AF2 function in tamoxifen-oestrogen receptor (TAM-ER) complex. partial agonistic activity of tamoxifen results from AF1 action and depends on the cell type and promotor to which the transcription complex is bound. Similarly to oestrogens, fulvestrant after binding to ER leads to splitting off accompanied proteins, but inhibits dimerisation and nuclear localisation of receptor, and intensifies its destruction. Binding of fulvestrant-ER complex to ERE is inhibited, as are both functions AF1 and AF2 as well as coactivator binding. Increased degradation of ER mediated by fulvestrant is possibly based on shutdown of ER activation by other mediators, e.g. dopamine, cAMP (cyclic adenosine 3',5'-monophosphate), or growth factors.

Differences in MoAs of SERM and fulvestrant explain the lack of enhancement of endometrium growth activity of the latter, observed in preclinical research. They also allow us to expect a lack of protective activity of fulvestrant on bone metabolism, circulation, and neuroendocrine systems, which can be experienced by premenopausal women. Therefore, only postmeno-

pausal patients were initially recruited to clinical trials assessing drug efficacy.

Howell et al. [3] assessed the pharmacokinetic and pharmacological profiles and anticancer activity of fulvestrant in 19 postmenopausal women with breast cancer, previously treated with tamoxifen. The drug was intramuscularly administered in an initial dose of 100 mg, and then 250 mg. In 13 patients clinical benefit was revealed, and median response duration was 25 months. Researchers noted that luteinising hormone (LH) and follicle-stimulating hormone (FSH) levels increased after tamoxifen discontinuation, and then stabilised, which suggests that the drug dose used in postmenopausal patients did not impact hypothalamic-pituitary axis. Additionally, there were no significant changes in serum levels of prolactin, sex hormone-binding globulin (SHBG), and lipids.

Robertson et al. [4] focused on drug impact on cancer cells and compared activity of fulvestrant and tamoxifen administered before radical surgery in postmenopausal women. They assessed expression of ER, progesterone receptor (PR), Ki67, and apoptotic index in cancer tissue samples taken before and after operation. Patients received intramuscularly a single dose of either fulvestrant (50 mg, 125 mg, or 250 mg) or tamoxifen 20 mg/day orally on days 14–21 before surgery or placebo masking tamoxifen. The effect of fulvestrant on decreasing of ER, PR, and Ki67 expression depended on the dose. There was significantly decreased ER expression observed for all doses as compared to placebo, but only for 250 mg comparing to tamoxifen. Doses of 125 mg and 250 mg led to decreasing of PR expression as compared to placebo, whilst tamoxifen increased receptor expression as compared to placebo. All fulvestrant doses caused decreasing of Ki67 expression as compared to placebo, but this effect did not significantly differ from the effect of tamoxifen. None of the fulvestrant doses stimulated changes of apoptotic index as compared to placebo or tamoxifen. This trail clearly indicates the relationship between the therapeutic effect of fulvestrant and its dose.

However, the following years saw interest in fulvestrant activity in treatment of premenopausal women. Robertson et al. [5] compared the effect of a single dose of 250 mg with placebo administered for 14–21 days before radical surgery. Again, changes of such parameters like ER, PR, and Ki67 expression in cancer tissue were assessed. There were no statistically significant differences in both patient groups, and the researchers concluded that the administered anti-oestrogen dose was probably too low for premenopausal patients. Young et al. [6] addressed this consideration and compared the efficacy of a single administration of 750 mg of fulvestrant with tamoxifen therapy for 14–16 days (20 mg) before radical surgery. In this case, statistically signifi-

cant decrease of ER and Ki67 was noted after treatment of both drugs as compared to baseline values. In both patient groups there was also a decrease in PR expression; however, it was statistically significant only in patients treated with fulvestrant. Changes of expression of selected markers were consistent among both groups. In patients treated with fulvestrant, increased oestradiol serum level was noted, regardless of the phase of menstrual cycle in which the drug was administered, but there were no significant changes in LH, FSH, and progesterone levels after either drug.

The cited trials focused researchers' interest on the dose of 250 mg of fulvestrant in postmenopausal patients. In parallel, they confirmed the assumption that in premenopausal women this drug is safe, but considering higher oestrogen blood levels the dose is insufficient and should be increased or combined with pharmacological castration [7].

### Early clinical trials with the dose 250 mg fulvestrant

In 2002 fulvestrant was registered in the US in the dose of 250 mg for the treatment of postmenopausal patients with advanced hormone-sensitive breast cancer, treated previously with anti-oestrogens. This marketing authorisation was based on clinical trials indicating that the drug's efficacy is non-inferior to anastrozole in this indication. Effects of treatment with fulvestrant in the dose of 250 mg in first, second, or further lines of palliative hormone therapy was investigated in multiple phase 2 and 3 clinical trials.

Howell et al. [8] compared the efficacy of fulvestrant and tamoxifen in first-line palliative treatment in a non-inferiority study. The researchers failed to prove that the new drug was not inferior to the drug from the SERM group as regards time to progression (TTP) and overall survival (OS).

Trial 0020 [9] and Trial 0021 [10] were pivotal trials for fulvestrant in second-line treatment after progression during or after anti-oestrogens. These trials showed that the efficacy of fulvestrant 250 mg (intramuscular injections once per month) in this indication is equal in efficacy to anastrozole 1 mg. Combined analysis of these trials, published after median follow-up of 15 months [11] and 27 months [12] indicates that medians of TTP are 5.5 vs. 4.1 months, medians of OS 27.4 vs. 27.7 months, and objective response rates (ORR) 19.2 vs. 16.5%, respectively, for fulvestrant and anastrozole.

Fulvestrant is also active in patients previously treated with third-generation aromatase inhibitors (AIs), and indicates equal efficacy to exemestane. Studies by Ingle et al. [13] and Chia et al. [14] indicated that in such patients (for 60–70% of patients it was the third line of

hormone therapy) a median TTP could be expected of 3–3.7 months, median OS — 20.2 months, and clinical benefit rate (CBR) — 32–35%. By contrast, in small clinical trials without control groups [15, 16], analysing the efficacy of fulvestrant in a patient after multiple lines of systemic treatment (2–7), it was indicated that this drug enabled median of TTP 3–6 months and CBR of 21–38%.

The efficacy of fulvestrant in combination with other hormones was also investigated. The FACT trail [17] indicated no differences as regards TTP or OS in a patient treated with fulvestrant combined with anastrozole as compared to anastrozole in first-line palliative hormone therapy (HT). On the other hand, the design of the SoFEA trail [18] was a little more complex. The patients with disease progression on NSAI were assigned to three therapeutic arms: fulvestrant + anastrozole vs. fulvestrant + placebo vs. exemestane. Particular schemes of hormone therapy indicated similar efficacy as regards progression-free survival (PFS) and OS.

Table 1 presents the details of clinical trials assessing the efficacy of fulvestrant in the dose of 250 mg.

### Comparison of efficacy of fulvestrant in the dose of 250 mg and 500 mg

Previous clinical trials assessing biological activity of a single dose of fulvestrant in patients before radical surgery have already indicated dose-dependency. Kuter et al. [19] compared the influence of fulvestrant in the doses 500 mg and 250 mg on cancer tissue in 211 postmenopausal patients. The drug was administered for 16 weeks before operation. Ki67, ER, and PR expressions were assessed in baseline biopsy, and then in week 4. of hormone therapy and finally after operation. In the fourth week of the treatment decreasing of Ki67 and hormone receptor expression was greater in the patients receiving higher doses of fulvestrant. However, in the 16<sup>th</sup> week of treatment the response rates assessed in primary tumour were similar and amounted 23 and 21% for the doses 500 mg and 250 mg, respectively.

Observations from clinical trials on neoadjuvant HT provided an impulse for the CONFIRM study; in postmenopausal patients who had previously received HT, the efficacy of fulvestrant in experimental dose of 500 mg (administered in day 0, 14, 28, and then every 28 days) and standard at that time dose of 250 mg (every 28 days) was compared [20]. Nearly half of the patients previously received AIs, and the remaining patients were treated with tamoxifen. Progression-free survival, the primary endpoint of the study, was statistically significantly longer in the group of patients receiving the drug in a higher dose, and medians were 6.5 vs. 5.5 months, respectively (HR 0.80; 95% CI 0.68–0.94;  $p = 0.006$ ).

Table 1. Clinical trials assessing the efficacy of fulvestrant in the dose of 250 mg in subsequent lines of palliative hormone therapy

Author	Trial phase	The line of hormone therapy	Study design	N	Treatment results
Howell, 2004	3	I	F vs. TAM Non-inferiority trial. in app. 20% of patients ER and PR status unknown	587	Median follow-up 14.5 months mTTP 6.8 vs. 8.3 months; p = 0.088; ORR 31.6 vs. 33.9%; p = 0.45 mOS 36.9 vs. 38.7 months; p = 0.04 "non-inferiority" of F as compared to TAM not met
Howell, 2002 Trial 0020	3	II	F vs. ANA 98% of patients treated previously with TAM App. 3.5% of patients ER/PR— App. in 20% of patients ER/PR status unknown	451	Median follow-up 14.4 months. mTTP 5.5 vs. 5.1 months; p = 0.84 ORR 20.7 vs. 15.7%; p = 0.2 CBR 44.6 vs. 45%
Osborne, 2002 Trial 0021	3	II	F vs. ANA 95% of patients treated previously with TAM App. 6% of patients ER/PR— In 7% of patients ER/PR status unknown	400	Median follow-up 16.8 months mTTP 5.4 vs. 3.4 months; p = 0.43 ORR 17.5 vs. 17.5%. CBR 42.2 vs. 36.1%
Robertson, 2003	3	II	F vs. ANA Analysis of combined Trials 0020 and 0021	851	Median follow-up 15.1 months mTTP 5.5 vs. 4.1 months ORR 19.2 vs. 16.5%
Howell, 2005					Median follow-up 27 months mOS 27.4 vs. 27.7 months; p = 0.809 less joint symptoms in patients treated with fulvestrant p = 0.0234
Chia, 2008 EFFECT	3	II or later	F vs. Exe Patients with disease progression after NSA1. 60% of patients after ≥ 2 lines of hormone therapy	693	mTTP 3.7 vs. 3.7 months; p = 0.65 ORR 7.4 vs. 6.7%; p = 0.74 CBR 32.2 vs. 31.9%; p = 0.85
Ingle, 2006	2	II or III	One-arm trial Patients with disease progression after AI. 73% of patients after 2 lines of hormone therapy	77	PR 14.3% SD 20.8% mTTP 3 months mOS 20.2 months
Mlineritsch, 2007		II–V	Single-arm trial Median of number of previous therapy lines — 2	54	Median of follow-up 19.4 months ORR 9.3% CBR 38.9% mTTP 6.4 months
Catania, 2007		II–VIII	Single-arm trial 27 patients receiving the drug after disease progression after chemotherapy. 30 patients receiving the drug as maintenance treatment after hormone therapy or chemotherapy	57	ORR 2% CBR 21% mTTP 3 months. No differences in efficacy of treatment between patients receiving the drug after disease progression and as maintenance treatment after hormone therapy or chemotherapy
Bergh, 2012 FACT	3	I	F+ANA vs. ANA 15 premenopausal women (3%) — received agonist of GnRH App. 66% of patients after adjuvant treatment with anti-oestrogens	514	mTTP 10.8 vs. 10.2 months; p = 0.91 mOS 37.8 vs. 38.2 months; p = 1.0
Johnston, 2013 SoFEA	3	II or III	F+ANA vs. F vs. Exe Patients with disease progression on NSA1 App. 70% of patients after previous treatment with TAM	723	mPFS 4.4 vs. 4.8 vs. 3.4 months F+ANA vs. F NS F vs. Exe NS mOS 20.2 vs. 19.4 vs. 21.6 months F+ANA vs. F NS F vs. Exe NS

F — fulvestrant; TAM — tamoxifen; ANA — anastrozole; Exe — exemestane; GnRH — gonadotropin-releasing hormone; HT — hormone therapy; ChT — chemotherapy; mTTP — median of time to progression; mOS — median overall survival; mPFS — median progression-free survival; ORR — objective response rate; CBR — clinical benefit rate; NS — non-significant; SD — stable disease

ORRs did not differ statistically significantly (9.1% vs. 10.2%), and in 45.6% and 39.6% of patients clinical benefits were noted for the dose of 500 mg and 250 mg, respectively. The subsequent results analysis, performed after 75% of patients died, indicated the superiority of higher fulvestrant dose as regards overall survival [21]; medians 26.4 vs. 22.3 months, respectively (HR 0.81; 95% CI 0.69–0.96,  $p = 0.02$ ). Additionally, there were no statistically significant differences as regards the tolerance of both doses and patients' quality of life (QoL) [20].

In 2010 these data were the base for registration of fulvestrant in the dose of 500 mg in postmenopausal women with advanced breast cancer, having disease progression or recurrence after treatment with anti-oestrogens.

### Clinical trials assessing the efficacy of fulvestrant in the dose of 500 mg

One of the more important studies published to date, assessing the clinical value of fulvestrant in the dose of 500 mg, is the phase 2 non-inferiority clinical trial FIRST. This study included postmenopausal patients with advanced breast cancer, previously not treated with palliative systemic treatment [22, 23]. In general, three quarters of patients did not previously undergo any hormone therapy. The patients received fulvestrant 500 mg IM (day 0, 14, 28, and then every 28 days;  $n = 102$ ) or anastrozole 1 mg orally ( $n = 103$ ). The clinical benefit rate, the primary endpoint of the study, indicated non-inferiority of fulvestrant 500 mg as compared to anastrozole (72.5% vs. 67%, OR 1.30; 95% CI 0.72–2.38;  $p = 0.386$ ) [22]. Secondary endpoints included, among others, ORR and TTP. Whilst ORR confirmed similar efficacy of both drugs (36% vs. 35.5%; OR, 1.02; 95% CI, 0.56–1.87;  $p = 0.947$ ) [22], time to progression was statistically significantly longer in the group of patients treated with fulvestrant (median 23.4 vs. 13.1 months, HR 0.66, 95% CI 0.47–0.92,  $p = 0.01$ ) [22, 23]. In this respect, after a longer observation period the study protocol was amended, and unplanned preliminary overall survival analysis was performed. Despite the mentioned limitations, this analysis indicated superiority of fulvestrant 500 mg (median 54.1 vs. 48.4 months, HR 0.7, 95% CI 0.50–0.98;  $p = 0.04$ ) [23]. No significant differences were noted regarding treatment tolerance, which was good in both arms. These data were confirmed in the phase III clinical trial FALCON [24], which included 462 postmenopausal patients previously not receiving HT due to breast cancer. The primary endpoint was progression-free survival. Fulvestrant seemed to be better than anastrozole (HR 0.80, 95% CI 0.64–1.00,  $p = 0.049$ ; median PFS 16.6 vs. 13.8 months). Particu-

lar benefits from fulvestrant treatment were noted in patients with metastases to other than parenchymal organs — in this group the relative progression risk was lower by nearly a half as compared to the patients treated with aromatase inhibitor (HR 0.59; 95% CI 0.42–0.84). Both drugs were similarly effective as regards objective response.

On the other hand, Ishida et al. [25] assessed the efficacy of fulvestrant 500 mg in 117 postmenopausal patients, after multiple lines of palliative systemic treatment (median number of previous HT lines — 2). The response rate was 8.5%, CBR — 41.9%, and median TTP — 6.1 months. The authors concluded that patients with acquired hormone-resistance could be good candidates for fulvestrant treatment, regardless of the number of previous lines of HT.

### Fulvestrant in premenopausal patients

There are scarce data on the efficacy of fulvestrant in palliative hormone therapy in premenopausal patients. During the 2005 ASCO Annual Meeting, Stager et al. presented a pilot study [26] assessing fulvestrant in the dose of 250 mg in this indication in combination with goserelin 3.6 mg in 14 patients, in which this treatment was indicated as effective and well tolerated. In 2012 Bartsch et al. [27] published the results of an observational study, including 26 premenopausal patients with advanced breast cancer. The patients received the same treatment as in the Stager study, cited above, within 1<sup>th</sup>–4<sup>th</sup> line. In total 80% of patients received previously tamoxifen, and 70% — AI in combination with goserelin, and in a similar percentage of patients metastases to parenchymal organs were diagnosed. Clinical benefit was reported in 58% of women, median TTP was six months, and median OS was 32 months, which indicates that a combination of fulvestrant and goserelin could also be a valuable therapeutic option in young patients.

The above-mentioned data from neoadjuvant trials assessing increasing doses of fulvestrant in premenopausal patients indicate that increasing the dose could contribute to better therapeutic affect also in younger patients.

### Adverse events during treatment with fulvestrant

Pivotal trials for the 250-mg dose of fulvestrant [9, 10] and the FIRST study with the dose of 500 mg [22] show that treatment tolerance is good and equal to anastrozole tolerance. The most common adverse reactions observed after the dose of 250 mg included

nausea (26%), weakness (22.7%), pain (18.9%), vasomotor disturbances (17.7%), and headache (15.4%). The local adverse reactions connected to the injection included pain, inflammation and bleeding, although usually mild or moderate. The prevalence of local symptoms depended on the method and volume of injection, and accounted for 1.1% in patients receiving single administration of 250 mg in 5-mL solution, and 4.6% for double injection with 2.5 mL [11]. Contrary to this, in patients treated with fulvestrant with the dose of 500 mg bone pain (13.9%), nausea (10.9%), joint pain (9.9%), constipation (9.9%), vomitus (8.9%), dyspnoea (8.9%), and hot flushes (7.9%) were noted; additionally, 5.9% of patients reported pain in the injection site (two injections of 250 mg) [22].

### Clinical trials assessing the combination of fulvestrant with molecularly targeted therapy

Primary and secondary hormone-resistance is a challenge for contemporary hormone therapy. There are a few theories regarding the mechanism of its development. The most important postulate emerging of the mutation of oestrogen receptor gene and interaction of this receptor with pathways involved in intracellular signal transduction. Among the latter the most important seem to be pathways engaged in transduction of activation from membrane receptors for growth factors, particularly PI3K/AKT/mTOR pathway (phosphatidylinositol-4,5-bisphosphate 3-kinase/AKT/mechanistic target of rapamycin) [28]. An important strategy aiming to reverse the mentioned mechanisms of hormone-resistance is the combining of hormone drugs with targeted therapies. Fulvestrant was used in multiple preclinical and clinical trials assessing this topic.

The study by Burstein et al. [29] was designed to answer the question of whether adding lapatinib to fulvestrant-based hormone therapy in patients with hormone-sensitive advanced breast cancer prolongs PFS. The study included 295 patients, regardless of HER2 status, previously treated with AIs, and 57% of them had also received tamoxifen. There were postmenopausal patients; however, the definition of menopause included also patients receiving agonist of gonadotropin-releasing hormone for at least three months before inclusion in the study. Patients received fulvestrant 500 mg IM on day 1, and then 250 mg on days 15 and 29, and every four weeks in combination with lapatinib 1500 mg/day or with placebo. No significant differences were noted between the groups of patients receiving fulvestrant with lapatinib and fulvestrant with placebo as regards PFS (medians 4.7 vs. 3.8 months, respectively, HR 1.04; 95% CI 0.82–1.33;  $p = 0.37$ ) and OS (HR 0.91; 95% CI

0.68–1.21;  $p = 0.25$ ). In general, 18% of patients were characterized with excessive HER2 expression; in this subgroup, adding lapatinib to hormone therapy numerically prolonged PFS (medians 5.9 vs. 3.3 months), but this difference was not statistically significant ( $p = 0.53$ ). Grade 3 adverse events were significantly more frequent in patients receiving lapatinib (19% vs. 5%;  $p = 0.001$ ), mainly as acne-like rash, diarrhoea, fatigue, and elevation of transaminase levels. Treatment discontinuations due to toxicities were also more frequent in this group (12% vs. 2%;  $p = 0.001$ ). Thereby, adding lapatinib to fulvestrant in this indication, especially in an unselected population as regards HER2 expression, does not give any additional benefit to the patients, but it is connected with more intense toxicity.

During the last San Antonio Breast Cancer Symposium (SABCS) the phase II PrECOG 0102 study was presented [30], which was aimed at assessing the effectiveness of fulvestrant combined with mTOR inhibitor. The study included 130 postmenopausal patients with metastatic breast cancer with expression of hormone receptors and HER2-negative, resistant to AI. Patients received fulvestrant combined with either everolimus or placebo. Combined therapy prolonged PFS (median PFS 10.4 vs. 5.1 months) at the expense of a higher number of grade 3/4 adverse events (53% vs. 23%); among them hyperglycaemia, stomatitis, lipids disturbance, lymphopaenia, and pneumonia were the most common.

On the other hand, the authors of the phase 2 FERGI study [31] assessed the efficacy of a combination of fulvestrant with the PI3K inhibitor pictilisib as regards PFS in postmenopausal patients with advanced breast cancer with hormone receptor expression, HER2-negative, and treated previously with AIs. The study contained two parts. To the first part 168 patients were included, regardless of the status of *PIK3CA* gene (*phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha*), and to the second part 61 patients were included with mutations of that gene. Activating mutations of *PIK3CA* gene occur in approximately 40% of HER2-negative breast cancer patients with ER expression. Unfortunately, their role in activating PI3K-dependent signal transduction pathway and development of hormone resistance is unclear. Patients received pictilisib orally (340 mg in part 1 and 260 mg in part 2 of the study) since day 15 of cycle 1, or placebo and fulvestrant 500 mg IM (standard dosing). There was no statistically significant difference regarding PFS between patients assigned to the treatment with pictilisib combined with fulvestrant and fulvestrant with placebo, neither in part 1 nor in part 2 of the study [median 6.6 months vs. 5.1 months, respectively; HR 0.74 (95% CI 0.52–1.06);  $p = 0.096$  and 5.4 months vs. 10 months; HR 1.07 (95% CI 0.53–2.18);  $p = 0.84$ ]. In patients treated with pictilisib grade 3 or more, adverse events were more frequently recorded,

especially in part 1 of the study (61 vs. 28%, respectively). They included mainly rash, diarrhoea, fatigue, hypertension, elevation of aminotransferase levels, and hyperglycaemia. Although subgroup analysis indicated that in patients with ER+ PR+ breast cancer (68% of patients) adding pictilisib to hormone therapy prolonged PFS [median 7.4 months vs. 3.7 months, HR 0.44 (95% CI 0.28–0.69);  $p = 0.0002$ ], investigations with the drug in this indication are not currently continued. The authors concluded that use of the drug was limited by its toxicity, which could impact the efficacy of the treatment.

The second drug from this group investigated in combination with fulvestrant is also administered orally: buparlisib — selective class I PI3K inhibitor, showing affinity to all four enzyme isoforms ( $p110\alpha$ ,  $-\beta$ ,  $-\delta$ , and  $-\gamma$ ) as well as its forms with somatic mutations of subunit  $p110\alpha$  (*PIK3CA*) [32]. The results of the phase 3 Belle-2 study [33] were presented during SABCS 2015. In total, 1147 postmenopausal patients with advanced HR+/HER2– breast cancer, resistant to AIs, were recruited to the study. Patients received fulvestrant in the dose of 500 mg in combination with buparlisib (100 mg/d) or placebo, administered since day 14 of therapy. Additionally, the activity of PI3K signal pathway was assessed, defined as mutation in *PIK3CA* or *PTEN* (*phosphatase and tensin homolog*) genes in archived tissue samples and status of *PIK3CA* gene in circulating tumour DNA (ctDNA) in 587 patients. Combined treatment prolonged PFS in the whole patient population (median 6.9 vs. 5.0, HR 0.78, 95% CI 0.67–0.89;  $p < 0.001$ ), in patients with *PIK3CA* mutation, detected in ctDNA (median 7.0 vs. 3.2, HR 0.56, 95% CI 0.39–0.80;  $p < 0.001$ ), in patients with activated PI3K pathway (median 6.9 vs. 4.0, HR 0.76, 95% CI 0.60–0.97;  $p = 0.014$ ), but not in patients with wild *PIK3CA* in ctDNA (median 6.8 vs. 6.8, HR 1.05, 95% CI 0.82–1.34;  $p = 0.642$ ). The most common grade 3 and 4 adverse events in patients treated with combination therapy and fulvestrant with placebo included, respectively: increase of ALAT (alanine aminotransferase) (26 vs. 1%) and ASPAT (asparagine aminotransferase) (18 vs. 3%) concentrations, hyperglycaemia (15 vs. 0.2%), and rash (8 vs. 0%). In 13% and 2% of patients, respectively, adverse events led to treatment discontinuation. This study showed not only the clinical value of buparlisib, but also some data indicated a predictive molecular marker for therapy. The results of the phase III Belle-3 study were presented during SABCS 2016 [34]. The study included 432 postmenopausal patients with breast cancer resistant to AIs and hormone therapy combined with mTOR inhibitor. Patients were randomly assigned to two arms, analogical to Belle-2 study. In this special patient group, superiority of combined therapy was indicated (median PFS 3.9 vs. 1.8 months), but this benefit was compromised by a significantly higher number of

adverse events, including elevation aminotransferase levels and psychiatric symptoms (anxiety, depression).

The aforementioned potential mechanisms responsible for development of resistance to hormone therapy (membrane receptors for growth factors, intracellular signal transduction pathways) converge in the place of activity of cyclin-dependent kinase 4 and 6 (CDK4 and CDK6). Therefore, considerable hopes were placed in inhibitors of these kinases, especially as some relationship between effective hormone therapy and activity of these enzymes was observed. This was not a disappointment — the idea of combining fulvestrant with selective CDK4/CDK6 inhibitor palbociclib was successful [28]. The drug is administered orally; it inhibits DNA synthesis through blocking of cell cycle transition from G1 to S phase. Combination of fulvestrant with CDK4/CDK6 inhibitor is disadvantageous to phosphorylation of suppressor Rb protein and eventually leads to long-lasting cell cycle inhibition. The phase 3 Paloma-3 study included 521 patients with HER2-negative advanced breast cancer with expression of hormone receptors, treated previously with hormones. A total of 40% of patients previously received AIs, 14% — tamoxifen, and 46% — both drugs. One-fifth of patients were premenopausal, and they received LHRH analogue. Patients received palbociclib in the dose of 125 mg/d for three weeks with one week break in a four-week cycle, together with fulvestrant in the dose of 500 mg (standard dosing) or placebo and fulvestrant. Median follow-up exceeded 15 months. Using combination therapy significantly prolonged PFS (median 11.2 vs. 4.6 months, HR 0.5, 95% CI 0.4–0.62,  $p < 0.0001$ ) [35]. Secondary endpoints include, among others, overall survival and safety. Recruitment to the study was prematurely stopped due to significant efficacy of experimental therapy; nevertheless, the study protocol did not allow the patients from the control group to cross over to experimental treatment, which could have enabled us to expect reasonable data regarding overall survival. In the group of patients receiving combination treatment more grade 3 and 4 adverse events were reported (73 vs. 22%), and the most common included neutropaenia (65 vs. 1%), anaemia (3 vs. 2%), and leukopaenia (28 vs. 1%). It should be noted, however, that neutropaenic fever episodes were noted in three patients (1%) with combined therapy and in one patient (1%) receiving fulvestrant with placebo [28]. Serious adverse events affected 13% of patients with combined therapy and 17% of patients from the group receiving fulvestrant with placebo [28]. Additionally, combination therapy enabled patients to maintain general quality of life, whilst in the group treated with fulvestrant and placebo it deteriorated substantially ( $p = 0.03$ ). Experimental treatment also enabled improvement of emotional functioning as compared to placebo ( $p = 0.002$ ) [36].

Moreover, the status of *PIK3CA* gene in circulating DNA was assessed in 395 recruited patients, and 33% were positive for mutation. No relationships were found between status of *PIK3CA* gene and treatment efficacy, as well as for expression level of hormone receptors and type of previous hormone therapy or response to it. Following the success of the phase 3 Paloma-2 study [37], in which palbociclib added to letrozole in first-line palliative hormone therapy increased median PFS by 10 months and decreased relative progression risk by 42%, Paloma-3 provides additional evidence that CDK4/6 inhibitors are a valuable therapeutic option for patients with positive expression of hormone receptors at different stages of hormone therapy.

## Conclusions

Fulvestrant is a drug known in Poland but used only in a small number of oncology centres, usually as a third or even further line of palliative hormone therapy. Some impediment in its usage is its restriction only to hospital treatment (the prescription drug is fully paid) and its price, which is significantly higher than other hormone drugs used in breast cancer patients. For example, analysis performed in United Kingdom showed no cost-effectiveness for the dose of 500 mg as compared to anastrozole using a standard threshold value of £ 20,000–30,000/QALY [38].

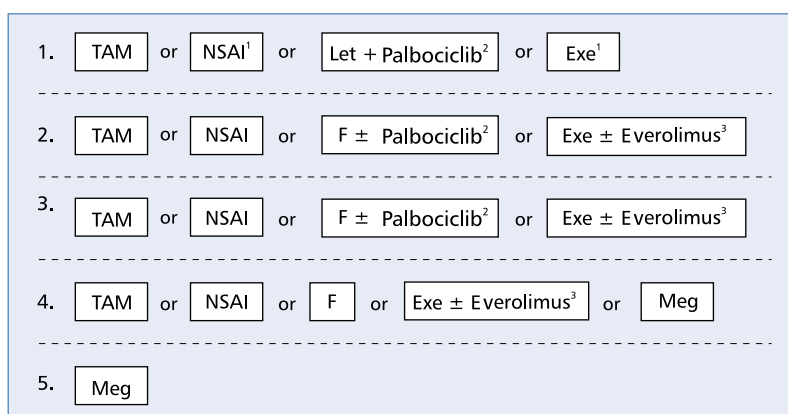
According to registered indications, fulvestrant is dedicated for the treatment of postmenopausal women with breast cancer showing positive expression of oestrogen receptors, locally advanced or metastatic, previously treated with anti-oestrogens, within adjuvant or palliative treatment. In this indication, the drug is not inferior to anastrozole. Additionally, recent clinical trials have shown greater efficacy of fulvestrant as compared

to anastrozole if the drug is used in first-line palliative treatment in patients previously not having received hormone therapy. The recommended dose of the drug is 500 mg, administered intramuscularly every month, with an additional dose of 500 mg two weeks after the first dose.

Fulvestrant is also an important therapeutic option in further lines of hormone therapy in postmenopausal and younger women, after artificially induced menopause with LHRH analogue. This drug is also a valuable partner for targeted therapies in combination treatment used for overcoming primary or secondary hormone resistance in breast cancer patients. Special hopes are connected with the combination of fulvestrant and CDK4/6 inhibitor — palbociclib, which decreased the risk of disease progression by half with good tolerance as compared to hormone therapy alone.

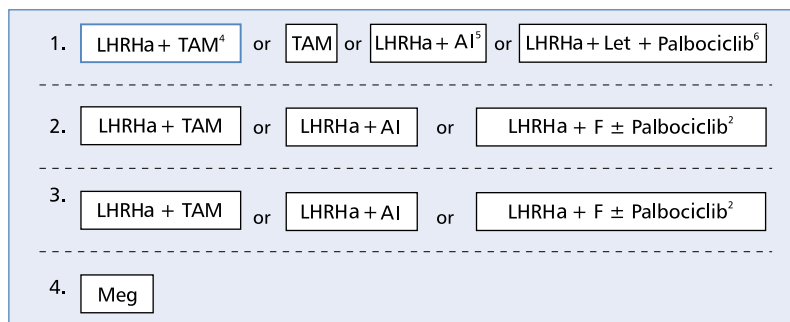
Thereby, fulvestrant is a highly valued option in the hormone drug armamentarium used in breast cancer patients, and ongoing clinical trials on its combination with targeted therapies indicate possible broadening of the indications to its use.

Figure 1 and 2 delineate proposed subsequent lines of hormone therapies in, respectively, postmenopausal and premenopausal patients with HER2-negative advanced breast cancer with expression of hormone receptors. In postmenopausal patients AIs are the preferred drugs in first-line palliative hormone therapy (cross-reference in Fig. 1). A meta-analysis of 31 clinical trials showed that compared to TAM treatment with AIs prolongs progression-free survival (HR 0.78, 95% CI 0.70–0.86) and increases clinical benefit (OR 0.70, 95% CI 0.51–0.97), but without any impact on overall survival [39, 40]. It should also be remembered that in Poland aromatase inhibitors are reimbursed in the second-line of hormone therapy. Palbociclib has been registered by the US FDA in combination with letrozole in first-line



**Figure 1.** Sequence of hormone therapy in postmenopausal patients with HR+HER2– breast cancer. HR — hormonal receptors; NSAI — nonsteroidal aromatase inhibitors; TAM — tamoxifen, F — fulvestrant; Meg — megestrol acetate; Let — letrozole; Exe — exemestane





**Figure 2.** Sequence of therapy in premenopausal patients with HR+HER2- breast cancer. LHRHa — luteinising hormone-releasing hormone analogue; AI — aromatase inhibitor

palliative hormone therapy since 2015, and in combination with fulvestrant after failure of previous hormone therapy since 2016 [28, 41] (cross-reference 2 in Fig.). On the other hand, everolimus has been registered in Europe and the US since 2012 for the treatment of advanced breast cancer with expression of hormone receptors, without excessive HER2 expression, in combination with exemestane, in postmenopausal women without symptomatic spreading to internal organs, after disease recurrence or progression after non-steroid aromatase inhibitor (cross-reference 3 in Fig.). In a phase 3 clinical trial combination therapy prolonged progression-free survival as compared to exemestane alone (centrally assessed median PFS 10.6 months vs. 4.1 months, respectively, HR 0.36; 95% CI 0.27–0.47;  $p < 0.001$ ) [42]. Patients included into this study were previously treated with NSAI (100%), tamoxifen (48%), or fulvestrant (16%).

In premenopausal women the optimal choice of drug within first-line hormone therapy is not established, but a meta-analysis including four clinical trials showed higher efficacy of combination treatment LHRHa + TAM as compared to LHRHa with regard to prolongation of overall survival ( $p = 0.02$ ; HR 0.78), progression-free survival ( $p = 0.0003$ ; HR 0.70), and objective response rate ( $p = 0.03$ ; OR 0.67) [41] (cross-reference 4 in Fig.). In this group of patients all options of hormone therapies available for postmenopausal patients could be used, providing that artificial menopause is induced (cross-reference 5 in Fig.). According to European marketing authorisation for palbociclib, this drug could be administered to the premenopausal and postmenopausal patients as a first or subsequent treatment line. Registration of palbociclib in first-line hormone therapy in combination with AI in premenopausal patients was not directly confirmed in a phase III clinical trial. In premenopausal patients, hormone therapy should be combined with LHRH analogue (cross-reference 6 in Fig.).

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