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REVIEW ARTICLE

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Wise and skillful utilization of contemporary endocrine therapies for the treatment of ER+/HER2– advanced breast cancer

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ABSTRACT

Endocrine therapy is one of the key and most frequently utilized strategies for breast cancer treatment, both in the early and advanced stages of the disease. Its activity relies on the presence of functional estrogen receptors in cancer cells, which are responsible for stimulating the survival and growth of breast cancer. Over the past four decades, endocrine therapy significantly has progressed not only due to the emergence of new drugs disrupting the estrogen receptor functions but also thanks to the development of new targeted agents that block intracellular mechanisms of hormone resistance.

The large number of endocrine therapies used either as monotherapy or in combination with other agents vary not only in their mechanisms of action but also their safety profiles. This diversity poses a big and continuously growing challenge in planning and conducting an optimal, multi-stage palliative hormonal treatment in clinical practice. This article aims to summarize current knowledge on contemporary endocrine treatment options and highlight the possibilities for making hormone therapies a truly personalized treatment for advanced breast cancer patients.

Keywords: endocrine treatment, estrogen receptor, alpelisib, CDK4/6i, mTOR, PIK3CA, breast cancer

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Introduction

Over the past few decades, endocrine therapy for advanced breast cancer (ABC) with luminal features and the absence of overexpression of HER2 receptor (ER+/HER2–) has been based on the sequential use of drugs that disrupt estrogen receptor (ER) function, either by ligand elimination or direct receptor inhibition. Inhibition of estradiol production can be achieved either by surgical/pharmacological ovarian function suppression or by blocking the androgen-to-estrogen conversion process (aromatization) with the use of an aromatase inhibitor (AI). In turn, a direct ER blockade could be achieved either by ER modulation (inhibition of ligand-binding affinity while maintaining minimal signaling activity) with the use of a selective estrogen receptor modulator (SERM) — tamoxifen or by receptor downregulation with a selective ER degrader (SERD) — fulvestrant, elacestrant, giredestrant [1]. For many years, there have been discussions on how to optimize endocrine treatment to increase its effectiveness and durability. The optimal therapy sequence was analyzed, and available drugs in various combinations were studied. However, significant progress appeared only after when hormone therapy was combined with drugs having other mechanisms of action [2–4]. The combination of

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AIs and fulvestrant with CDK4/6 inhibitors, which are phase-specific antiproliferative drugs, resulted, for the first time in many years, in significant improvement of ER+/HER– ABC patients prognosis of advanced ER+/HER2– BC patients [4–7]. At the same time, numerous, relatively small academic studies were evaluating the possibility of combining classical metronomic chemotherapy with hormone therapy. These studies also suggested meaningful clinical activity of endocrine/chemotherapy combinations in advanced ER+/HER2– ABC [8, 9]. Undoubtedly, however, enormous progress in systemic therapy of hormone-dependent breast cancers has been made as a result of the characterization of molecular mechanisms responsible for endocrine sensitivity and resistance and the exploitation of defined targets in clinical practice [10]. One of the first discoveries immediately translated into clinical practice was understanding the interaction between ER and HER2 receptors [11]. In the following years, various PI3K-AKT-mTOR signaling pathway-targeting drugs emerged [12–14], and novel irreversible ER inhibitors with the potential to inhibit the mutated estrogen receptor (*ESR1*) are on the horizon [15, 16]. This review intends to present basic molecular mechanisms responsible for endocrine sensitivity and resistance and discuss current approaches to exploit these mechanisms in clinical practice to optimize systemic endocrine treatment of ABC ER+/HER2– patients.

Endocrine sensitivity

The majority of breast cancers (BC) express ER and progesterone receptor (PR), which play a crucial role in the biology of normal breast cells and breast cancer cells. Estradiol and progestogens, which regulate the physiology of the mammary gland, also play a critical role in the stimulation of progression, survival, invasiveness, and metastasis of breast cancer cells. Endocrine therapy is utilized to deactivate the function of steroid receptors by preventing the ligand-receptor interaction (systemic elimination/deprivation of the ligand or blockade of the receptor's ligand-binding domain). Although both ER and PR have been shown to play an essential role in stimulating cellular processes, the only effective therapeutic options available in clinical practice are based on ER inhibition by using drugs that directly block this receptor (SERM, SERD) or inhibit estradiol production (aromatase inhibitors, GnRH analogs). The PR-targeted therapeutic modalities are currently limited to the sporadic use of progestogens, which can induce apoptosis of cancer cells through receptor hyperstimulation. Still, the experience with this strategy to date is scarce [17, 18]. Therefore, in the rest of this article, the term "endocrine treatment" will be understood as pharmacological treatment aimed at blocking ER-related tumorigenic activities.

Endocrine sensitivity of BC (hormone dependence) is a consequence of the role of ER in breast cancer cell biology. The higher the percentage of tumor cells expressing ER and the higher the level of ER expression in tumor cells, the higher the expected endocrine sensitivity [19]. According to the standards of pathological evaluation, lack of expression of steroid receptors is defined as ER and PR expression in $\leq 1\%$ of tumor cells. However, from a tumor biology perspective, ER expression in $\leq 10\%$ of tumor cells strongly indicates a lack of endocrine sensitivity. The role of PR in BC cell biology is much less clear. PR expression is commonly believed to depend on a functional ER because the activity of ER-based transcriptional complex drives PR expression. Thus, the lack of PR expression in ER++ cells indicates a potentially limited impact of ER on tumor biology and, consequently, a lower endocrine sensitivity [20].

Resistance mechanisms

It is generally believed that highly hormone-sensitive BC cells are well differentiated, with low/moderate growth dynamics and limited potential for visceral dissemination [21]. Therefore, in ER+ BC high grade, a high proliferation rate (high Ki67) suggests relatively lower endocrine sensitivity [22]. This situation is often observed in ER+ cancers overexpressing HER2, where, despite high ER expression, high tumor grade and a high proliferative rate are observed, and endocrine therapy alone is usually not sufficient to achieve effective and long-term disease control.

Role of HER2 receptor

Available evidence indicates a bidirectional interaction between the ER- and HER2-associated signaling pathways, leading to cell cycle progression, proliferation, survival, and increased invasiveness [23, 24]. HER2 overexpression causes both *de novo* and acquired endocrine resistance. For example, long-term culture of ER+ breast cancer cells in the presence of fulvestrant or tamoxifen leads to increased HER2 and EGFR expression [25], and an increased HER2 signaling pathway activity can activate ER independently of estradiol, resulting in the development of endocrine-therapy resistance [26]. Approximately 20% of breast cancers that initially do

not overexpress HER2 may achieve the state of overexpression during the course of the disease [27]. Activating mutations in the gene encoding HER2 (*ERBB2*), which may appear in ER+ breast cancer cells exposed to endocrine treatment, confer endocrine resistance but are susceptible to HER2 tyrosine kinase inhibitors (TKIs) [28]. On the other hand, ER activity contributes to the development of resistance to anti-HER2 targeted therapies. Wang et al. demonstrated that HER2 blockade by lapatinib leads to increased ER expression and increased activity of ER-dependent signaling pathways, which in turn contribute to the development of acquired resistance to lapatinib [29]. There are two different ways by which estrogens exert their effects inside the cell: a) nuclear/genomic activity, in which the ER binds to transcription factors and co-regulators (CoA/R) to modulate gene expression; b) extranuclear/extragenomic activity, in which ER interacts directly or indirectly with membrane receptors for epidermal growth factors (EGFR, HER2-4) and activates their signaling pathways, for example PI3K-AKT-mTOR or RAS-RAF-MEK-ERK pathways [23]. Additionally, HER2 signaling pathways can reduce ER expression, while ER can promote the expression of the *ERBB2* gene and other genes encoding various membrane receptors and their ligands [23, 24]. This interaction appears to be a key mechanism responsible for the resistance of HER2+/ER+ BC to single-agent HER2- or ER-targeting therapies [24].

ESR1 mutations

Another important mechanism of endocrine resistance is the mutation of the *ESR1* gene, which encodes the ER alpha (ERα). Primary *ESR1* mutations in early BC without prior exposure to hormone treatment are relatively rare (approx. 3%) [30]. On the other hand, acquired activating *ESR1* mutations occur in over 30% of BC patients undergoing AI-based therapy [31]. Acquired *ESR1* mutations are detected less often during treatment with ER-targeting drugs such as tamoxifen or fulvestrant. *ESR1* mutations usually occur in codons 537 and 538 and are responsible for a change in the conformation of ERα, which enables constant activity of this receptor despite the absence of its ligand — estradiol [30]. The presence of *ESR1* mutations is associated with a worse prognosis in ABC patients, regardless of the type of systemic treatment used (endocrine therapy or chemotherapy). In the SOFEA study, *ESR1* mutations were associated with a worse prognosis, yet the anti-tumor potential of fulvestrant was significantly higher than that of exemestane [32]. Additionally, a PADA study showed that early switching from AI to fulvestrant with continuation of palbociclib in patients with *ESR1* mutation detected in circulating tumor DNA (ctDNA) was associated with a marked improvement in progression-free survival (PFS) [33].Novel oral SERDs demonstrated higher activity than standard endocrine approaches in BC with *ESR1* mutation [34]. Also a novel SERM (lasofoxifene) have been shown to provide benefit in the case of *ESR1* mutation [35].

Dysregulation of the PI3K-AKT-mTOR signaling pathway

One of the most essential mechanisms determining endocrine resistance is dysregulation of the intracellular PI3K-AKT-mTOR signal transduction cascade. This pathway, transmitting signals from activated membrane receptors to the cell nucleus, may interact with nuclear or cytoplasmic/membrane-bound ER at various levels. The PI3K-AKT-mTOR pathway plays a vital role in cell cycle control, cell growth, and survival, as well as in the control of protein synthesis and glucose metabolism [36–38]. The consequence of this intracellular interaction results in a bidirectional crosstalk leading to the activation of the PI3K-AKT-mTOR pathway by ER and activation of ER-dependent nuclear mechanisms by the PI3K-AKT-mTOR pathway. Thus, increased activity of the PI3K-AKT-mTOR pathway may lead to the activation of ER-dependent tumor mechanism even in the case of effective pharmacological blockade of ER. In recent years, several therapeutic strategies targeting the PI3K-AKT-mTOR pathway have been evaluated in ABC ER+/HER2-patients.

One of the first drugs with proven activity in this setting was an inhibitor of serine-threonine kinase mTOR — everolimus. In the phase III study (BOLERO-2), the combination of everolimus with exemestane in ER+/HER2– ABC patients after failure of previous endocrine treatment was found to be significantly more active than exemestane + placebo combination [12]. Median PFS was 10.6 and 4.1 months in the everolimus and placebo arms, respectively, which translated into a significant reduction in the relative risk of progression by 67% [hazard ratio (HR) = 0.36; 95% confidence interval (CI) 0.27–0.47]. However, everolimus did not significantly improve overall survival (OS) (HR = 0.89; 95% CI 0.73–1.10), with a median OS of 31.0 months (everolimus) and 26.6 months (placebo).

Capivasertib, an AKT serine-threonine kinase inhibitor, was evaluated in the phase III CAPITELLO-291 trial in ABC patients who failed up to two lines of endocrine therapy and one line of chemotherapy (approximately 70% of patients had previously received

a CDK4/6 inhibitor) [14]. A total of 708 patients were enrolled in the study, 41% of whom had dysregulations of the PI3K-AKT-mTOR pathway (including 76% of patients with a *PIK3CA* mutation). The use of capivasertib in combination with fulvestrant resulted in a significant reduction in the relative risk of progression both in patients with AKT pathway dysregulations (HR for PFS = 0.5; 95% CI 0.38–0.65) and in the general population irrespectively of AKT-status (HR for PFS = 0.6; 95% CI 0.51–0.71). The use of capivasertib was associated with a significant increase in objective response rate (ORR) in the general population (22.9% *vs.* 12.2% in the placebo group). The probability of obtaining an objective response (OR) was almost twice as high in the population of patients with AKT pathway dysregulations (OR = 3.93) than in the general population (OR = 2.19).

Endocrine treatment combined with PI3K-AKT-mTOR pathway blockade available in clinical practice in Poland

The only currently available reimbursed drug that inhibits the activity of the PI3K-AKT-mTOR signaling pathway is the small-molecule PI3K kinase inhibitor — alpelisib. This drug selectively inhibits the activity of the p110 catalytic subunit of PI3Kα kinase encoded by both the wild-type and mutated *PIK3CA* gene [39]. Thus, alpelisib has suppressor activity in relation to both *PIK3CA* mutation-mediated and upstream membrane receptor-mediated (e.g. by HER2) PI3K activation. The phase III SOLAR-1 trial compared the effectiveness of the alpelisib and fulvestrant combination with the fulvestrant + placebo combination [40]. The study included 572 patients, of whom 341 had a confirmed *PIK3CA* mutation. The use of alpelisib was associated with a significant reduction in the relative risk of progression in patients with the *PIK3CA* mutation (HR for PFS = 0.65; 95% CI 0.50–0.85), with median PFS of 11.0 months (alpelisib) and 5.7 months (placebo) and a significant increase in the ORR (26.6% *vs.* 12.8% for the alpelisib and placebo, respectively). In patients without *PIK3CA* mutations, the use of alpelisib was not associated with a significant improvement in PFS. The final results of the SOLAR-1 study did not show significant differences in OS in patients with the *PIK3CA* mutation, with median OS of 39.3 and 31.4 months, in alpelisib and placebo arms, respectively.

Adverse events associated with the use of alpelisib and other PI3K-AKT-mTOR-targeting drugs in clinical practice

The most common adverse events and suggestions for primary prevention and therapy are presented in Table 1.

Hyperglycemia

All molecularly targeted drugs disrupting the PI3K-AKT-mTOR signaling pathway demonstrate class-specific adverse events (AEs). As this pathway plays a key role in the regulation of cellular glucose metabolism both in cancer and normal cells, blocking its function leads to systemic metabolic disorders. The PI3K-AKT-mTOR pathway transmits signals from insulin receptors in hepatocytes, which induces glycogenesis disorders in the case of its inhibition [36]. In the SOLAR-1 study, alpelisib was associated with hyperglycemia in 63% of patients, including grade G3 and G4 hyperglycemia in 33% and 4%, respectively [40]. In the control arm, hyperglycemia was observed in 10% of patients, including grade G3 and G4 in approximately 0.5% of patients.

Table 1. Typical adverse events of PI3K-AKT-mTOR pathway inhibitors — prevention and treatment principles

Adverse event	Management before treatment initiation	Prevention	Treatment
Hyperglycemia	Assessment of fasting glucose level and HbA1c	Metformin starting from 1 × 500 mg/day	Diabetology consultation
Diarrhea	Medical history — diarrhea? Intestinal diseases? Drugs with diarrheagenic potential?	Patient education	Loperamide from the first episode of diarrhea
Stomatitis	None	Patient education	Rinsing of the oral cavity with an aqueous solution of dexamethasone 1 mg/10 mL 4 times a day for 2 minutes
Rash	None	Antihistamines once daily for the first 8 weeks of therapy	Antihistamines twice a day + topical steroids

HbA1c — glycated hemoglobin

In turn, in the BOLERO-2 study, hyperglycemia occurred in 13% of patients (grade ≥ G3 in 5%) in the arm receiving everolimus and exemestane and in 2% of patients in the exemestane + placebo arm [12]. The use of capivasertib in the CAPITELLO-291 study induced hyperglycemia in 16% of patients (grade ≥ G3 in 2%) compared to 3.7% of patients in the placebo arm [14].

According to current recommendations, in patients qualified for therapy with drugs disrupting the PI3K--AKT-mTOR pathway, it is recommended to initially assess glycemic control based on fasting glucose and glycated hemoglobin HbA1c levels and monitor these parameters during treatment. In patients receiving alpelisib, it is possible to use hyperglycemia prophylaxis based on metformin, used from the beginning of therapy with a PI3K inhibitor at an initial dose of 500 mg/day, escalated to 3 × 500 mg/day [41]. All patients with ineffective glycemic control should be consulted by a diabetologist.

Diarrhea

Diarrhea is another typical AE associated with PI3K--AKT-mTOR signaling pathway-targeting agents. In the SOLAR-1 study, diarrhea occurred in 58% of patients (grade G3 in 7%) receiving alpelisib in combination with fulvestrant and 16% receiving placebo with fulvestrant. In turn, the use of everolimus in the BOLERO-2 study was associated with the occurrence of diarrhea in 30% of patients, and the use of capivasertib in the CAPITELLO-291 study induced diarrhea in 72% of patients (including grade G3 in 9%). The diarrhea is a consequence of the apoptosis-related disappearance of crypt cells and granulocyte-mediated inflammation within the crypt epithelium [42]. Before initiating the PI3K-AKT--mTOR-targeting agent inhibitor, it is necessary to analyze the patient's medical history to identify those with chronic diarrhea or co-occurring diseases or therapies that may predispose to this AE. Discontinuation or replacement of medications that potentially cause diarrhea should be considered. Patients should also be informed about the risk of diarrhea and appropriate management. In addition, loperamide should be introduced from the beginning of the alpelisib-based therapy or when the first episode of diarrhea occurs [41].

Stomatitis (inflammation of oral mucous membrane)

Inhibition of the PI3K-AKT-mTOR pathway is often associated with inflammation of the oral mucosa (stomatitis). In the SOLAR-1 study, this adverse event occurred in 25% of patients (grade G3 in 2.5%) taking alpelisib, compared to 6% of patients in the arm receiving placebo [40]. Similarly, in the CAPITELLO-291 study, capivasertib caused stomatitis in 15% of patients (grade G3 in 2%) compared to 5% of patients receiving placebo [14]. In the BOLERO-2 study, 56% of patients in the everolimus + exemestane arm experienced stomatitis (grade G3 in 8%) compared to 11% of patients in the placebo arm [12]. Due to the very high incidence of stomatitis in patients receiving everolimus stomatitis-prevention methods for patients treated with the mTOR inhibitor have been established almost a decade ago. In the phase II SWISH study, patients rinsed their mouths with a non-alcoholic solution of dexamethasone (1 mg/10 mL) from the onset of everolimus treatment. Rinsing (for 2 minutes) was performed four times a day for eight weeks [43]. After this period of treatment, stomatitis occurred in only 2% of patients.

Due to the relatively lower frequency of stomatitis in patients treated with alpelisib compared to everolimus, there is no justification for primary prevention. Still, dexamethasone-based mouthwash should be introduced as soon as the first symptoms of stomatitis appear, e.g., single aphthous ulcers.

Skin toxicities

Other typical AE of PI3K-AKT-mTOR pathway-blockers are rash, maculopapular pruritus, and dry skin. When alpelisib was used in combination with fulvestrant, it occurred in 36% of patients (including G3 in 10%), compared to 6% of patients receiving fulvestrant alone [40]. The incidence of rash in patients receiving everolimus is the same as for alpelisib (36% of patients, but G3 only in 1%) [12]. Capivasertib caused a rash in 38% of patients, including G3 in 12% [14]. The rash is induced by activation of eosinophils and histamine-producing cells [44]. An increase in PBMC eosinophils was observed in patients with rash, which may indicate the predictive value of this parameter related to rash occurrence in clinical practice. Rash in patients receiving alpelisib appears within the first two weeks of therapy (median time to onset — 12 days). The preventive use of antihistamines in patients participating in the SOLAR-1 study significantly reduced the risk of this AE (reduction from 54% to 27% — any grade) as well as of G3 (12% instead of 20%) [40].

Optimization of systemic treatment of patients with ER+/HER2– ABC

One of the most critical stages of chronic systemic treatment of advanced cancer patients is the selection

of the optimal first-line treatment. In clinical practice in Poland, the choice of first-line therapy in many cases is determined by the current reimbursement policy of the National Health Fund; however, in the case of ER+/ /HER2– ABC patients, the access to world standard therapies for 1st line treatment is not an issue. Therefore since all accepted treatment options are readily available two basic questions regarding the optimal first-line treatment of ABC ER+/HER2- patients exists: a) chemotherapy or endocrine therapy? and b) endocrine therapy alone or in combination with a CDK4/6 inhibitor?

Chemotherapy or endocrine therapy?

The use of chemotherapy in the first-line treatment of advanced ER+/HER2– BC must be considered in patients requiring an immediate and profound treatment response, which most often results from imminent life-threatening organ crisis [45]. Usually, this situation occurs in patients with massive, metastatic liver involvement and signs of liver failure (hyperbilirubinemia, coagulation disorders, transaminase activity > 5 × ULN). The only treatment option in such patients is immediate initiation of chemotherapy based on drugs without liver clearance — cisplatin or carboplatin and gemcitabine [46]. One of the safest and most active regimens in this situation is the combination of gemcitabine with cisplatin (gemcitabine 1000 mg/m^2 + cisplatin 25 mg/m^2 on days 1. and 8. every 21 days). However, in most patients with liver involvement, only a slight elevation of liver enzymes may be initially observed [increase in transaminases and gamma-glutamyltranspeptidase (GGTP) activity] without any evident symptoms of liver failure (hyperbilirubinemia, hypoalbuminemia, coagulation disorders). In that case, the choice of a proper systemic treatment should first consider the chances of achieving an objective response to chemotherapy or intensified (by combination with CDK4/6i) endocrine therapy. High grade of malignancy (G3), high Ki67 proliferation index (> 40–50%), and low potential endocrine sensitivity [small percentage of ER+ cells or low ER expression level (1+)] are important arguments to consider the implementation of chemotherapy [19, 22]. On the other hand, low grade, low proliferation index, and high and widespread ER expression in cancer cells support endocrine therapy. The phase II RIGHT Choice study compared doublet chemotherapy with endocrine treatment (AI ± aLHRH) combined with ribociclib in previously untreated patients with aggressive, advanced ER+/HER2– breast cancer [47]. Disease aggressiveness was described as the occurrence of symptomatic organ metastases or rapid progression threatening organ function or significant, asymptomatic clinical stage. The study included 222 patients meeting the above disease aggressiveness criteria, with Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2 and with bilirubin serum level not exceeding 1.5 × ULN. The use of endocrine agents in combination with ribociclib was associated with a significantly higher median PFS compared to chemotherapy (24 months *vs.* 12.3 months with HR = 0.54; 95% CI 0.36–0.79) with a similar rate of objective responses and disease control. It should be highlighted, however, that patients with high-grade breast cancer (G3) accounted for 28.8% of the study population. In the majority of patients, breast cancer showed potentially very high endocrine sensitivity [PR expression in 90.5% of patients, and high (> 50% of cells) ER expression in 85.5% of patients]. Therefore, there is no doubt that the RIGHT Choice study indicates the advantage of endocrine therapy in combination with CDK4/6i over chemotherapy but mainly in patients with massively advanced but potentially very endocrine-sensitive and relatively well-differentiated breast cancer without co-occurring signs of severe organ failure [47]. However, the above indication does not constitute clear recommendations in clinical practice but should rather be considered as suggestions resulting from many years of observations and retrospective analyses.

Endocrine therapy alone or in combination with CDK4/6 inhibitor?

When CDK4/6 inhibitors combined with endocrine therapy showed a significant improvement in the prognosis of ABC ER+/HER2– in both first and second-line, discussions began about the optimal utilization of CDK4/6i in sequential systemic treatment. Many arguments have been raised for the validity of using these drugs from the very beginning of palliative treatment as part of the first-line therapy, pointing to significantly longer survival (number of months) compared to second-line treatment. On the other hand, it was indicated that the relative benefit of using CDK4/6 inhibitors is the same in the first and second treatment lines. Still, the duration of adverse events is potentially much longer if these drugs are used in the first line. The results of the phase III SONIA study seemed to put this debate to rest finally. This study included 1050 ER+/HER2– ABC patients who had not yet received palliative systemic treatment and were not at risk of organ crisis [48]. Patients were randomized in a 1:1 ratio to arm A receiving first-line AI and then, after progression, fulvestrant in combination with CDK4/6i of the

physician's choice (abemaciclib, ribociclib, palbociclib) or to arm B receiving AI + CDK4/6i in first-line and then, after progression, fulvestrant alone. As expected, the use of AI + CDK4/6i in the first line was associated with a significant improvement in PFS compared to AI monotherapy. However, the time to second progression (PFS2 — time from randomization to failure of second-line treatment) and OS did not differ significantly between the study arms (HR for PFS2 = 0.87; 95% CI 0.74–1.03 and HR for OS = 0.98; 95% CI 0.80–1.20). The SONIA study not only demonstrated the lack of advantage of the use of CDK4/6i in the first line compared to second-line settings but also showed a 42% increased incidence of G3–4 adverse events in patients receiving CDK4/6i in the first line. Additionally, the cost of treatment based on CDK4/6i in the first line was $200,000 higher than the use of these drugs in the second treatment line.

When should CDK4/6 inhibitors be used in first-line treatment?

The use of CDK4/6i increases the activity of endocrine therapy not only in terms of PFS but also in terms of response. In the MONALEESA-2 study, ribociclib increased the ORR from 28 to 41% [49], which was similar to the activity of abemaciclib in the MONARCH 3 (from 37% to 50%) [50] and palbociclib in the PALOMA-2 study (from 35% to 42%) [51]. There is no doubt that the increased probability of response is extremely important in symptomatic patients or patients with potentially highly endocrine-sensitive breast cancer with visceral metastases, in whom there are no clear indications for chemotherapy. As previously mentioned, in the majority of ABC patients participating in the RIGHT Choice study, which demonstrated a significant advantage of endocrine therapy in combination with ribociclib over doublet chemotherapy, the patient population seemed to be enriched with highly endocrine sensitive tumors (grade G1–G2, ER expression > 50%, PR expression) [47]. In symptomatic and high-risk patients, the implementation of highly active first-line systemic treatment allows for fast and profound tumor response, which instantly diminishes disease-related symptoms and risk of aggravating organ dysfunction.

The use of CDK4/6i in first-line treatment is also extremely important in breast cancer patients with *PIK3CA* mutation. An activating mutation of the *PIK3CA* gene occurs in approximately 40% of patients with ER+/ /HER2– breast cancer [37]. Although in the case of early breast cancer, the presence of a *PIK3CA* mutation may be associated with an improved long-term prognosis [52], patients with advanced ER+/HER2– breast cancer harboring *PIK3CA* mutation have an unfavorable prognosis in terms of both PFS and OS [53]. The presence of *PIK3CA* mutations also seems to be an unfavorable predictor of response to endocrine therapy, regardless of whether it is used in curative or palliative setting [54]. Therefore, assessing *PIK3CA* gene status is necessary for optimal planning of the first-line endocrine treatment because it identifies patients with a worse prognosis related to high probability of primary endocrine resistance. Patients with ER+/HER– ABC diagnosed with the *PIK3CA* gene mutation should receive AI in combination with CDK4/6i upfront (first-line treatment), and then, in the case of treatment failure, a combination of fulvestrant and alpelisib (Fig. 1).

Treatment after AI + CDK4/6i failure in ABC patients without *PIK3CA* mutation

Fulvestrant alone in second-line treatment in *PIK3CA-intact* ER+/HER2– ABC patients after failure of AI + CDK4/6i combination has demonstrated modest effectiveness. All attempts to increase its efficacy by combining fulvestrant with continuing CDK4/6i beyond 1st line did not support this concept. Nevertheless, for asymptomatically progressing patients, fulvestrant monotherapy is still a valuable therapeutic approach. However, in many symptomatic patients or individuals with visceral progression, endocrine therapy alone does not represent the optimal choice and is often replaced by standard chemotherapy despite the fact that tumor may be still responsive to endocrine treatement. One option to postpone the use of chemotherapy in such cases would be the use capivasertib and fulvestrant combination, which in the general, molecularly-unselected population of the CAPITELLO–291 study showed a 2-fold higher ORR (19.4%) compared to fulvestrant alone (8.5%) [14]. If capivasertib is unavailable, the combination of fulvestrant with metronomic chemotherapy may represent an interesting and active option instead of standard chemotherapy administered typically at maximum tolerated doses [55]. The possibility of combining endocrine therapy with chemotherapy as a part of palliative treatment, evaluated in several small clinical trials and retrospective analyses, has demonstrated excellent safety profile with evident clinically activity. In a single-arm phase II clinical trial, 41 ABC chemotherapy-naïve patients after a single line endocrine treatment received metronomic capecitabine combined with fulvestrant [8]. This combination resulted in an ORR and disease-control

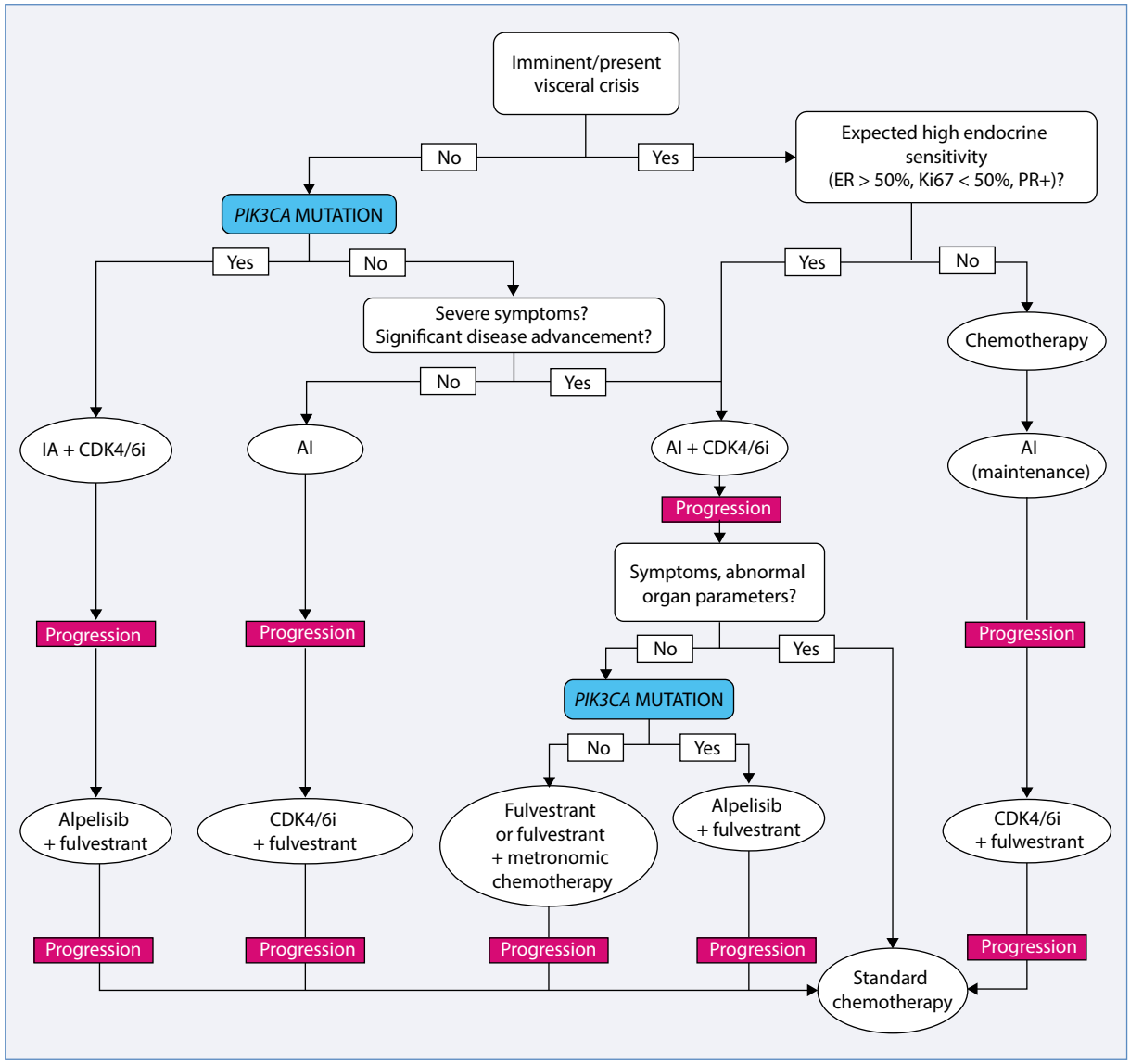

Figure 1. Algorithm of treatment in patients with advanced ER+/HER2– breast cancer. Early assessment of *PIK3CA* gene status plays a key role in optimizing hormone therapy; AI — aromatase inhibitor; CDK4/6i — CDK4/6 inhibitor; ER — estrogen receptor; PR — progesterone receptor

rate of 24.5% and 58.5%, respectively. Median PFS and OS were 14.98 and 28.65 months, respectively, which compares quite favorably with the results of key clinical trials with 2nd line CDK4/6 inhibitors. Treatment was well tolerated, with palmar-plantar erythrodysesthesia (PPE) being the most common grade 3 AE reported in 7.3% of patients. In a retrospective analysis by Aurilio et al. [56], the combination of fulvestrant with metronomic chemotherapy (cyclophosphamide plus methotrexate) was assessed in 32 heavily pre-treated patients with ER+ ABC. Concomitant administration of these drugs resulted in one partial response and disease stabilization in 17 patients (53%), demonstrating promising clinical activity along an excellent safety profile. In a phase II clinical trial, Rashad et al. evaluated the combination of capecitabine-based chemotherapy with hormone therapy (letrozole or tamoxifen) in first-line treatment in 40 patients with ABC ER+/HER2– [57]. Concomitant use of these drugs was associated with an ORR and clinical benefit rate in 60% and 82.5% of patients, respectively. Median PFS and OS for the general study population were 10.0 and 23.3 months, respectively. In patients treated with the capecitabine and letrozole combination, these medians were higher (by 4.0 and 3.0 months,

respectively) than for the capecitabine and tamoxifen combination. In a retrospective analysis conducted at the Jagiellonian University — Medical College Hospital in Krakow, 39 patients with previously treated, advanced ER+/HER2– breast cancer received a FulVEC regimen based on the combination of fulvestrant with metronomic polychemotherapy [capectabine 3 × 500 mg/day *per os* (*p.o.*), vinorelbine 40 mg *p.o.* 3 times a week and cyclophosphamide 50 mg/day *p.o.*] [58]. The majority of patients (74%) had previously received at least three lines of systemic treatment, including endocrine therapy and chemotherapy (77% of patients had previously been treated with at least one cytotoxic agent included in the FulVEC regimen). The clinical benefit rate (CBR) was 87% in the overall population, and median PFS and OS were 8.5 and 25.5 months, respectively. Comparing the obtained results with available data on the use of standard chemotherapy at the late stage of systemic treatment (e.g. capecitabine) [58], the effectiveness of FulVEC in terms of CBR, TTP/PFS, and OS seems to be much better. Moreover, none of the patients discontinued treatment due to drug toxicity, but 46% underwent subtle dose modifications of individual cytotoxic drugs depending on the specific adverse event.

Conclusions

There is no single standard therapeutic path for the treatment of ABC ER+/HER2– patients. Optimization of endocrine treatment must be based on detailed evaluation of symptoms, medical history verification, comprehensive assessment of laboratory and imaging tests, as well as characterization of critical tumor biological features that may affect the effectiveness of the planned systemic treatment. In the case of endocrine therapy, it is extremely important to determine the *PIK3CA* gene status before deciding on the first-line treatment strategy. Unknown status of this gene at the initiation of first-line treatment may result in the suboptimal choice of treatment in asymptomatic patients with the *PIK3CA* mutation or conversely on the choice of CDK4/6i+endocrine therapy combination that may be to intensive for first-line treatment with potential impact on quality of life of ABC patients without *PIK3CA* gene mutation.

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Supplementary material

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