ESR1 mutation as potential predictive marker for choice of treatment tactics in hormone–resistant HR+/HER2–negative breast cancer

I. V. Kolyadina, I. V. Poddubnaya

Russian Medical Academy for Postgraduate Continuous Education; National Medical Research Centre for Obstetrics, Gynecology and Perinatology n.a. academician V.I. Kulakov; Moscow, Russia

Summary

The analysis of current treatment strategy of advanced HR+/HER2-negative metastatic breast cancer (MBC) was performed, the criteria of hormone sensitivity and hormone resistance were determined, and the changes in tumor classification were reflected with due account for level of expression of estrogen receptors. The detailed characteristic of a new potential marker of acquired hormone resistance – activating somatic mutation of estrogen receptor gene, ESR1, leading to constitutive ligand-independent activity of estrogen receptor, was defined; the predictive and prognostic role of ESR1 mutation, its association with clinical course and response to hormone therapy was described. The studies on the search of optimal treatment regimen after progression on CDK4/6 inhibitors, including in the case of ESR1 mutation occurrence, were presented. The characteristic and key benefits of chemotherapy with eribulin in patients with hormone-resistant MBC were defined, the preliminary results of EMPOWER study on the potential of eribulin use after progression during the treatment with CDK4/6 inhibitors were presented. The present review will help to define the concept of patient-specific approach to the selection of treatment strategy in cases of hormone-resistant MBC.

Key words: ***advanced breast cancer, hormone sensitivity criteria, primary and secondary hormone resistance, progression on CDK4/6 inhibitors, ESR1 mutation, chemotherapy in the case of HR+/HER2-negative BC, treatment with eribulin after progression on CDK4/6 inhibitors.***

The breast cancer (BC) is the dominant oncopathology in the world both in the incidence and mortality rate [1, 2]. Moreover, most tumors are represented by luminal HER2-negative BC subtype, when the endocrine therapy is pathogenetically defined treatment option both at the early and advanced stages [3]. In case of metastatic breast cancer (MBC), the problem of drug selection is due to many factors: menstrual status, previous treatment and duration of response to it as well as neoplastic process symptoms and signs. According to recommendations of Russian and World Cancer Societies, the sequential use of up to three lines of endocrine therapy is recommended for patients with potentially hormone sensitive tumors, in case of absence of indications for immediate chemotherapy (visceral crisis symptoms), and then in case of response absence – switch to chemotherapy [4–6].

Hormone sensitivity criteria in cases of HR+/HER2-negative BC

In cases of HR+/HER2-negative MBC, the definition of *hormone sensitivity* and *hormone resistance* was changed significantly over recent years, which also requires re-thinking of approaches to individualization of treatment. Traditionally, *hormone-sensitive (hormone-positive)* tumors were considered to be the tumors, in which the nuclear expression of receptors of estrogens and/or progesterone (ER/PR) ≥ 1% was detected during the immune histochemical study; and in such case the endocrine therapy was recommended for patients including cases of MBC [4–6]. However, recent studies have raised doubts about such approach; it was shown that the course and prognosis of disease in patients with positive but low ER expression (ER-low – 1–10% of positively stained nuclei) is more unfavorable and the advantage of hormonal treatment is not so significant as in patients with ER expression >10% [7, 8]. According to the data of large meta-analysis with enrollment of 21,457 patients, the hormonal treatment with tamoxifen during five years substantially reduces the risk of disease recurrence (during first 5 years – by 47%, during next 5 years – by 32%; $p < 0.00001$) and risk of death (during first 5 years by 29%, during next 5 years – by 33%; $p < 0.0001$) in cases of ER+ BC, but not in patients with low ER expression [8].

Moreover, patients with low ER expression (ER-low) demonstrate good response to neoadjuvant chemotherapy (high complete pathologic responses rate) and in cases of residual tumor – the same poor prognosis as patients with triple-negative cancer [7–10]. The possible explanation of this phenomenon may be the results of the B.S. Sheffield *et al.* study, according to which the tumors with low ER expression (3–5 on Allred score, according to immune histochemical study) are the true luminal cancers only in 10% of cases with genetic analysis PAM50 and have genetic profile of basal-like or HER2-enrich subtypes in 90% of cases [10].

For this reason, the expert panel of ASCO/CAP Guideline Update 2019 recommended that patients with ER-low should be separated into the separate group, which will allow these patients to optimize the treatment policy. As the immune histochemical assessment of ER/PR status is the only one routine test-predictor of potential response to endocrine therapy, the panel ASCO/CAP Guidelines Update 2019 reminds of necessity of interpretation of analysis of steroid hormone receptor expression in cases of BC with the indication in per cent of positively stained nuclei and intensity of their staining [9]. The separation of ER-low BC into a separate group (tumors with doubtful hormone sensitivity) is supported by ABC 5 consensus, recommendations of NCCN and AGO in 2020; the oncologic communities emphasize that patients with MBC with low ER expression (ER-low) should not be discussed only for endocrine therapy, and the role of chemotherapy is significant for this group of patients [5, 11].

Hormone resistance criteria in cases of HR+/HER2-negative BC

As early, the consensus of international experts on advanced breast cancer ABC-3 has defined the concepts of primary and secondary hormone resistance depending on terms of progression onset [12].

Primary hormone resistance (hormone refractoriness) – disease progression during first 2 years from the beginning of adjuvant hormone therapy or first 6 months from the beginning of first-line hormone therapy for advanced BC.

Secondary (acquired) hormone resistance – disease progression two years later after the beginning of adjuvant hormone therapy or during the first year after its completion, or after 6 months from the beginning of first-line hormone therapy for advanced BC. It is worth noting that the definition of concepts of primary and secondary hormone resistance was proposed by consensus ABC-3 for simplification of clinical studies, but not for preparation of treatment plan in routine practice [12]. For determination of treatment strategy, it is necessary to accept the fact of progression as the indicator of *hormone resistance*, as in such situation it is necessary to change the hormone therapy (or switch to chemotherapy, in case of visceral crisis development or ineffectiveness of three sequential hormone therapy lines). Apart from this, the determination of *hormone sensitivity* means not only the presence of ER/PR expression in tumors, but also the clinical situations with disease progression after one year and more after the completion of adjuvant hormone therapy; in this situation, current endocrine agents are most effective and re-induction by means of previously used regimes is possible [12].

Current standards of treatment of HR+/HER2-negative BC

The endocrine therapy is biologically effective treatment strategy in cases of HR+/HER2-negative MBC; introduction of new class of drugs (cyclin-dependent kinase inhibitors, CDK4/6) has set priorities in treatment of patients with hormone-dependent tumors. Due to unique mechanism of anti-tumor activity, the drugs of this class (palbociclib, ribociclib and abemaciclib) have substantial advantages both in comparison to endocrine monotherapy [13]. The excellent combination of high efficacy, fast realization of anti-tumor response, controlled safety profile and, above all, convincing win in survival rate made the combined endocrine therapy with CDK4/6 inhibitors the preferable choice in the first- and second-line therapy of HR+/HER2-negative MBC [14–23].

The efficacy of representatives of CDK4/6 inhibitors class is proved demonstratively in the series of large randomized studies both in patients with potentially hormone-sensitive tumors (first line of MBC treatment) and in patients with hormone-resistant cancer (second line of MBC treatment and early relapses during not less than 12 months after adjuvant therapy) [13–23]. However, what calls attention to itself is that the efficacy of one and the same treatment regimens differs in these clinical groups. For instance, in the first-line treatment in patients with hormone-sensitive BC in 6 large II–III phase randomized studies (PALOMA-1/2, MONALEESA-2/-3/-7, MONARCH-3), the significant increase of median progression-free survival (PFS) (up to 20–37 months) is demonstrated, Δ 9–14 months – compared to control group [13, 15, 17, 18, 19, 21]. However, the combined therapy with CDK4/6 inhibitors in patients with hormone-resistant BC (second line of MBC treatment and early relapses after adjuvant treatment) demonstrates lower survival rates, although the differences in comparison to control group remain statistically significant [13, 14, 21–23]. For example, median PFS is 9.5–16.4 months after combination of fulvestrant with palbociclib/ribociclib/abemaciclib as the second-line treatment [13, 23].

The differences in CDK4/6 inhibitors efficacy in patients with hormone-sensitive and hormone-resistant MBC are clearly demonstrated in the large randomized MONALEESA-3 study. 726 patients with HR+/HER2-negative MBC were enrolled in the study and received the combination of ribociclib + fulvestrant *vs.* placebo + fulvestrant (367 patients – as the first-line treatment, 345 patients – as the second-line treatment of MBC + early relapses) [14, 23]. In both groups (first- and second-line treatment), the advantage of addition of ribociclib to fulvestrant is obvious, although absolute survival rates differ greatly between the groups. For instance, in the group of hormone-sensitive cancer (first-line treatment), median PFS was in favor of treatment with ribociclib and amounted 33.6 *vs.* 19.2 months, HR = 0.546, as well as OS (median was not reached *vs.* 45.1 months, HR = 0.700). In the group of the second-line treatment + early relapses after adjuvant treatment, ribociclib also showed significant benefit, but the survival rates were considerably lower – median PFS was 14.6 *vs.* 9.1 months, HR = 0.571; median OS – 40.2 *vs.* 32.5 months, HR = 0.730 [14, 23]. Accordingly, one and the same treatment regimen leads to different survival rates in patients with hormone-sensitive and hormone-resistant HR+/HER2-negative MBC [23]. It seems that the molecular genetic mechanisms of hormone resistance preclude from the full realization of anti-tumor potential of current endocrine agents. The study of mechanisms of acquired hormone resistance development is a critical oncologic challenge, as it will offer the possibility to plan effectively the strategy of treatment of HR+/HER2-negative MBC and to make the right choice (whether to continue the further endocrine therapy or prefer chemotherapy) after progression on CDK4/6 inhibitors.

ESR1 mutation as a new predicative and prognostic marker of acquired hormone resistance in cases of HR+/HER2-negative MBC

The crucial role in acquired hormone resistance development may be played by activating point mutations of estrogen receptor gene *ESR1*. Although *ESR1* was studied comprehensively as early as in the 90s of the past century, the significance of this phenomenon for development of resistance to endocrine therapy became actively studied only in recent years [24–26].

ESR1 is a gene located on 6-th chromosome and encoding estrogen receptor alpha, transmembrane protein, which plays a significant role in BC carcinogenesis. The estrogen receptor has C-terminus, ligand (estrogen) binding site and N-terminus, which contains several domains contributing to increase of transcriptional activity of some genes. The mutations in *ESR1* gene are somatic and may be presented by gene amplification or deletion, but particularly the point activating mutations, as a rule, in ligand binding

domain are responsible for development of constitutive ligand-independent activity of receptor. Moreover, the vast majority of mutations detected in cases of advanced breast cancer occur in ligand-binding domain ER with a 'hotspot' in sequential amino acids L536, Y537 and D538, which belong to the loop connecting α-helixes 11 and 12. The structural analyses show that these residues control the state of agonists of ligand-binding domain and contribute to transcription of ER-dependent target genes [24–26].

The impact of mutation presence in ligand-binding domain *ESR1* on its capability to become active under the influence of estrogen was studied comprehensively in the series of laboratory studies with the use of cell lines of BC [25–27]. For example, *in vitro* experiment of the D.R. Robinson *et al.* study, genes with *ESR1* mutations were cloned and introduced into HEK293T cell lines, which carry reporter element with response to stimulation by estrogens. In the cells without *ESR1* mutations, the reporter remained inactive in the absence of estrogen; however, in the cells with *ESR1* mutation the reporter was constitutively active and only weakly complementary activated in response to treatment by β-estradiol [25].

In another study (A. Harrod *et al.*) on the MCF7 cell lines with genomic encoding ER-Y537S (with built-in mutation of *ESR1*), the ligand-independent recruiting ER and gene expression regulation were noted in the absence of estrogen. Moreover, these cell lines of BC grew in the absence of estrogen and demonstrated dose-dependent resistance to antiestrogens [26]. Even more unexpected results were obtained in the study of R. Jeselsohn *et al.*; cell lines of BC with *ESR1* mutation demonstrate not only ligand-independent functions, which imitate activities of estradiol in cases of wild type *ESR1*, but also exhibit allele-specific neomorphic properties, which contribute to pro-metastatic phenotype [27].

It's clinically important that the point activating mutations of *ESR1* in ligand-dependent domain do not occur practically in cases of primary breast cancer, but are observed in 20–50% of cases during progression with previous endocrine therapy, thus the occurrence of *ESR1* mutation in patients with recurrent HR+/HER2-negative BC is the indicator of acquired hormone resistance based on onset of capacity for ligand-independent functions in tumorous clone [28, 29].

The somatic *ESR1* mutation may be determined by PCR method or NGS both in tumor samples taken during metastasis biopsy and in blood by means of genetic analysis of circulating tumor DNA [30–33]. It was shown that the point mutations in *ESR1* are mainly represented by mutations Y537S, D538G, E380Q, Y537N, Y537C, the vast majority of which are the first two mutations – Y537S and D538G; it is to be noted that half of *ESR1* mutations are polyclonal [30–32]

The recent studies allowed to determine the probabilistic portrait of patient with *ESR1* mutation in tumor. It includes patients with recurrent breast cancer (progression after early-stage treatment or metastatic disease treatment) previously received aromatase inhibitors. According to the data of X. Li *et al.*, 89% of patients with *ESR1* mutation had previous endocrine therapy with aromatase inhibitors [30]. The study by Y. Kuang *et al.* showed similar results: *ESR1* mutation was detected in 30% of patients with HR+/HER2-negative MBC, where 7% has no previous therapy with aromatase inhibitors, 32% received aromatase inhibitors for the treatment of early BC, and 42% used aromatase inhibitors for both adjuvant treatment and MBC therapy; $p = 0.016$ [31].

In 2020, the results of pilot study of Chinese authors were presented, which are of greatest clinical significance [30]. The authors carried out the genetic monitoring of *ESR1* mutation occurrence in blood samples and compared the mutational profile with the samples of histological biopsy in 45 patients with MBC; the genetic analysis was performed by NGS method with inclusion of 425 genes. It demonstrated that *ESR1* mutation detection rate in cases of advanced BC is the same in blood and tumor tissue samples, which is very important in the clinical practice, because it offers the possibility to conduct the genetic testing for the presence of mutation even in patients with metastatic lesions, which are not available for biopsy. The maximum mutation detection rate was shown in the case of previous endocrine therapy with aromatase inhibitors (17.8%), where the median from treatment onset to occurrence of *ESR1* mutation in blood was 39 months. Most importantly, the detection of *ESR1* mutation in blood preceded clinical and radiographic progression [30]. Therefore, the occurrence of *ESR1* mutation in patients with HR+/HER2-negative BC during endocrine therapy may indicate a high probability of hormone resistance development that will inevitably lead to the disease progression, and detection of *ESR1* mutation in the blood/tumor may become relatively soon the important predicative test for selection of treatment policy.

In recent years, a series of works on the study of *ESR1* mutation distribution rate in patients with different metastatic sites was presented. During the analysis of metastatic tumor samples in 77 Brazilian patients with BC in the study conducted by T. Reinert *et al.*, the prevalence of *ESR1* mutation was significantly higher in patients with visceral disease (25.0%) compared to non-visceral metastases (6.7%). The authors note that *ESR1* mutation was detected in different metastatic sites, including pleura, liver, lungs, ovaries, lymph glands, bones, and thoracic wall [28].

In cases of BC with *ESR1* mutation, the characteristics of sites of metastasis are clearly described in 2020 in *the Breast Cancer Research* [29]. The authors assessed the prognostic role of *ESR1* mutation in recurrent and primary metastatic BC. The analysis included the tumor samples of patients with distant metastases and loco-regional recurrences. In the group of patients with distant metastases, *ESR1* mutations were detected in 10/62 cases (16%), where 9/10 mutations were in D538G, and 1/10 was in L536R. Most frequently, *ESR1* mutations were detected in liver metastases (40%) and bone metastasis (30%); in the case of other localizations (skin metastases, mediastinal lymph nodes, and brain), the *ESR1* mutation detection rate did not exceed 10%. The authors also noted the prognostic significance of detected genetic changes: in patients received aromatase inhibitors, the time to progression in the presence of mutation was significantly shorter compared to patients with the absence of mutation (ESRwt) – 3 *vs.* 15 months, HR = 3.1; $p = 0.017$. In group of patients with loco-regional recurrences, the *ESR1* mutation detection rate reached 36% (15/41 cases), where D538G mutation prevailed in 14/15 patients and Y537C mutation was detected only once. During

analysis of clinical cases with repeated local recurrences, the authors note not only the occurrence of new *ESR1* mutations in recurrent tumors, but also the cases of *ESR1* mutation copying in primary tumor and next two local recurrences after 7 years and at 16 years [29].

The similar results are demonstrated by other authors; among patients with *ESR1* mutations, patients with liver metastases (88.2%) and bone metastases (97.1%) prevail, while pulmonary metastases are observed only in 38.2% patients with somatic activating *ESR1* mutation; $p < 0.0001$ [30, 31].

Prognostic role of *ESR1* mutation and selection of treatment strategy in cases of hormone-resistant HR+/HER2-negative MBC

The occurrence of *ESR1* mutation and resulting acquisition of hormone resistance (capacity to ligand-independent functions) by tumor negatively impact on further disease progression and make the selection of the further treatment strategy (to continue endocrine therapy or to prefer chemotherapy) is highly tentative.

The prognostic role of activating *ESR1* mutation in hormone-resistant MBC was studied in the series of large randomized studies. In the BOLERO-2 study, the blood analysis for *ESR1* mutation was performed in 541 patients with HR+/HER2-negative MBC with progression during endocrine therapy with aromatase inhibitors; the activating mutations detection rate reached 28.8%, where 21.1% of patients had D538G mutation, 13.3% – Y537S mutation; double mutation D538G and Y537S was observed in 5.5% of patients. The presence of mutation was associated with the worst overall survival rates (OS): in case of mutation absence, the median reached 32.1 months, and in case of its presence the median was only 20.7 months, HR = 1.62; $p < 0.001$. Moreover, median OS was 26 months with D538G mutation, 20 months with Y537S mutation, and with both mutations (D538G и Y537S) the median was critically low – only 15 months, HR = 2.23; $p < 0.001$. Addition of everolimus to exemestane reduced risk of further progression both in the ESRwt group and in patients with D538G mutation, but the negative impact of *ESR1* mutation on progression-free survival (PFS) rates is still significant. For example, in the group of treatment with exemestane, median PFS was 3.94 months (in case of ESRwt) and only 2.69 months with D538G mutation (HR = 1.71; $p = 0.02$). Addition of everolimus to exemestane resulted in significant increase of PFS: up to 8.5 months (HR = 0.4) in the ESRwt group and up to 5.8 months (HR = 0.34) in patients with D538G mutation [32].

The mechanism of anti-tumor activity of fulvestrant involves its potential activity in cases of *ESR1*-mutated BC. As fulvestrant is a 'pure' antiestrogen and facilitates the irreversible disaggregation of estrogen receptor, the presence of mutation and, therefore, the ligand-independent stimulation of estrogen receptor should not have impact on its efficacy [33]. This assumption was confirmed by SoFEA randomized study, in which the efficacy of treatment with fulvestrant was compared with exemestane treatment in cases of HR+/HER2-negative MBC. *ESR1* mutation was in 39.1% of cases and associated with advantage in PFS of fulvestrant over exemestane (5.7 *vs.* 2.6 months; HR = 0.52; $p = 0.02$). By contrast, the regimes in the ESRwt group were comparable in respect of efficacy: PFS was 8 months with exemestane and 5.4 months with fulvestrant, HR = 1.07; $p = 0.77$ [33]. However, in other study (PALOMA3) the advantage of combined endocrine therapy with CDK4/6 inhibitor, palbociclib, over monotherapy with fulvestrant was noted in cases of *ESR1*-mutated previously treated HR+/HER2-negative MBC. In the randomized phase III PALOMA-3 study, 360 patients had mutation in blood tests prior to the treatment; *ESR1* mutation was in 25.3% of cases. In patients with mutation presence, median PFS reached 9.4 months with combined endocrine therapy with palbociclib + fulvestrant, while in the group of fulvestrant + placebo the median was only 3.6 months, HR = 0.43, $p = 0.002$. It is interesting to note that patients without mutation had similar advantage in therapy with CDK4/6 inhibitor: 9.5 *vs.* 5.4 months, HR = 0.49; $p < 0.001$. Consequently, fulvestrant has potential efficacy in patients with *ESR1* mutation as compared to aromatase inhibitors but benefit from combination of fulvestrant and CDK4/6 inhibitors is more significant in this clinical situation [33].

What should be the treatment policy in patients receiving combined endocrine therapy with CDK4/6 inhibitors when acquiring *ESR1* mutation status in the absence of signs of recurrence, and what treatment regimen may be the optimal option of further therapy with presented progression? This question is the most difficult one, and it was actively discussed at the 2020 ASCO conference.

According to design of PADA-1 study, the results of which were reported at 2020 ASCO, it included two phases; the first phase involved 1,017 patients with HR+/HER2-MBC treated in the first-line treatment with palbociclib plus aromatase inhibitors (AIs) [34]. The blood test for *ESR1* mutation was performed before treatment, after 1 month of treatment, and then every 2 months; in case of detection of mutation without signs of progression, patients were switched to the second phase and randomized to two groups: 1) group of continuation of treatment with palbociclib + aromatase inhibitors or 2) group of palbociclib + fulvestrant. In statement of progression fact, patients were also switched to palbociclib + fulvestrant. If the median observation was 21.2 months, 452 of 1,017 patients enrolled in the study (44.4%) continued treatment with palbociclib + AIs, had no *ESR1* mutation and no progression; 565 patients (55.6%) withdrew from the first phase. Moreover, in 135 patients (24.0%) *ESR1* mutation emerged in blood, although progression was not observed (these patients were randomized to two treatment groups), and the progression was detected in 354 patients (62.7%) [34].

The authors note that the 'starting' *ESR1* mutation was observed in 3.2% of patients (33 of 1,017). The presence of such mutation was associated with previous adjuvant endocrine therapy with aromatase inhibitors (HR = 3.0), menopausal status (HR = 5.4), bone metastases (HR = 3.4), and low PFS rates in comparison with patients without mutation (11 *vs.* 26.7 months, HR = 2.3; $p < 0.001$). The most unfavorable prognosis was in patients with 'starting' mutation and mutation acquired during 1 month of therapy; in this situation, PFS rates were only 7.4 months, while in patients without mutation in the blood analysis (baseline or during the first month of therapy), PFS reached 24.1 months; $p < 0.001$ [34]. Consequently, the first results of PADA-1 study demonstrated unfavorable predictive and prognostic role of *ESR1* mutation in cases of HR+/

HER2-negative MBC; the follow-up will determine reasonability of continuation of combined therapy with CDK4/6 inhibitors + fulvestrant in case of mutation status occurrence.

The second study presented at 2020 ASCO was the PEARL study, phase III study of efficacy of combined endocrine therapy with CDK4/6 inhibitors versus chemotherapy (capecitabine) in patients with *ESR1* mutation [35]. The study included patients with progression during AIs treatment, which were divided into 2 cohorts: cohort 1, 296 patients,– randomized for therapy with palbociclib + exemestane *vs.* capecitabine; cohort 2, 305 patients,– randomized for therapy with palbociclib + fulvestrant *vs.* capecitabine. *ESR1* mutation was detected in blood of 29% of patients and was the independent unfavorable prognostic factor: survival rates were significantly lower in patients with mutation compared to ESRwt, PFS – 7.2 *vs.* 9.3 months, $p = 0.07$; OS – 25.4 *vs.* 34.3 months; $p < 0.0001$. It is important that combined endocrine therapy compared to the chemotherapy with capecitabine had no advantages in patients with *ESR1* mutation, and the life time of patients with detected *ESR1* mutation did not exceed 30 months irrespective of treatment regimen (palbociclib + exemestane, palbociclib + fulvestrant or capecitabine) [35].

Consequently, the results of first randomized studies confirm that *ESR1* mutation may become a new independent unfavorable predictive and prognostic marker in cases of HR+/HER2-negative MBC; moreover, currently there are no convincing data on advantage of endocrine therapy continuation in this clinical situation, that is why the search of optimal action plan in case of *ESR1* mutation detection becomes the objective of great relevance. Unfortunately, at present, routine genetic testing of blood/tumor tissue for presence of *ESR1* mutation is not included in the obligatory diagnostic plan of BC, and it is possible to guess the presence of activating *ESR1* mutation in patients only with the help of probabilistic 'portrait' of patients and specific course of disease.

Potential of eribulin use in cases of hormone-resistant MBC

Eribulin is a microtubule polymerization inhibitor, a synthetic analogue of halichondrin B, with the unique combination of high anti-tumor activity and favorable safety profile, offering the possibility to use it in patients with BC previously treated with anthracyclines and taxanes. Eribulin has a direct cytostatic action (it prevents tumor-cell division by formation of non-functional tubulin aggregates, decreasing the speed and degree of tubulin polymerization and interrupting formation of mitotic spindle, which cause a delay of tumor cells in the G2-M phase of cell cycle and apoptosis stimulation) and unique non-mitotic effects (remodeling of tumor vasculature, reversion of epithelial-mesenchymal transition, and reduction of ability of tumor cells to migration and invasion) [36–40]. Such wide range of anti-tumor activities lead to statistically significant increase of overall survival in comparison with any other therapy selected by the doctor; apart from this, eribulin is unique in that it is effective in case of different biological subtypes, including cases of HR+/HER2-negative MBC after progression during previous therapy with CDK4/6 inhibitors [39, 40].

As shown earlier in the PEARL study, the efficacy of combined therapy with palbociclib did not compare favorably with capecitabine in respect of PFS and OS in cases of *ESR1*-mutated BC [35]. However, particularly for eribulin in the phase III, randomized EMBRACE study, the advantage in statistically significant increase of overall survival was proved (13.2 *vs.* 10.5 months; $p = 0.014$) in patients received minimum two lines of treatment in comparison with therapy selected by the doctor [40]. Moreover, the convincing data are available (results of subgroup analysis of randomized study 301 published in 2018), which demonstrate the increase of median OS in the eribulin group compared to capecitabine in patients with HER2-negative MBC during the second-line therapy (16.1 *vs.* 13.5 months; $p = 0.026$) [41]. This explains high interest in study of potential of eribulin use in patients with hormone-resistant MBC with progression during the treatment with CDK4/6 inhibitors.

In 2019, the results of the large American observational study EMPOWER were presented, in which the efficacy and safety of eribulin in patients after progression during treatment with CDK4/6 inhibitors was analyzed; the analysis included 395 patients with HR+/HER2-MBC received CDK4/6 inhibitors (palbociclib – 88.4%, ribociclib – 6.8%, or abemaciclib – 3.5%) in combination with different endocrine preparations as the first and second line of treatment [30]. The median response to the therapy with CDK4/6 inhibitors was 9.7 months, median observation from the beginning of the first-line therapy – 12.4 months [36, 42].

Depending on prescription of eribulin, all patients were divided into four cohorts: 1) the drug was used as the second-line therapy, 121 patients (30.6%); 2) eribulin was used in the third line, 111 patients (28.1%); 3) eribulin was prescribed in accordance with the registered indications of FDA the USA, 135 cases (34.2%); 4) the drug was used in the fourth and further lines without previous treatment with anthracyclines and taxanes, 28 patients (7.1%). The cohort 3 ($n = 135$) is of great interest with the use of eribulin in accordance with the indications registered the USA (third-line chemotherapy of MBC after anthracyclines and taxanes). It is worth noting that the patients of this cohort had visceral disease in 92.6% (liver metastases – 51.9%, lungs – 56.3%) and brain damage was detected in 6.7% of patients [36, 42].

The first preliminary results of eribulin efficacy in the EMPOWER study are presented for 87 patients (64.4%): objective response (partial) is observed in 36 patients (26.7%), clinical benefit – in 73 patients (54.1%), disease progression is registered in 14 cases (10.4%), in 48 patients (35.6%) treatment efficacy with eribulin was not assessed by the time of analysis performance. It is important that in despite of extremely high ratio of patients with visceral metastases, median PFS was not reached in the treatment with eribulin and 6-month PFS was equal to 70.4%. The treatment safety profile was favorable and complied with previously presented data: neutropenia level was low – 23.0% of cases (febrile neutropenia only in 0.7% of cases), peripheral polyneuropathy was observed in 11.1% of cases, and diarrhea – in 12.6% of patients. The primary prevention of neutropenia (colony-enhancing factor support) was required in 11.9% of cases [36, 42].

Consequently, the preliminary results of the EMPOWER study demonstrated good combination of high efficacy of eribulin therapy in patients with hormone-resistant BC after progression

during the treatment with CDK4/6 inhibitors and favorable safety profile of the treatment. For instance, the drug efficacy was demonstrated in patients with visceral metastases that is very important in the clinical practice. Without doubt, the efficacy of the treatment with eribulin in the case of *ESR1* mutation presence was not studied separately, but most likely the ratio of patients with mutation status in the EMPOWER study should be sufficient in view of previous treatment of patients. The future studies will set a priority in treatment algorithm in patients with hormone-resistant BC with the presence of activating *ESR1* mutation; however, the results of the EMPOWER study hold out a hope that eribulin may become a high-potential treatment option in patients with hormone-resistant MBC after progression during the combined endocrine therapy with CDK4/6 inhibitors.

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