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Analysis of the efficacy and safety of eribulin therapy in patients with HR+/HER2- metastatic breast cancer pretreated with CDK4/6 inhibitors in real Russian practice

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Abstract

Relevance. Data on the efficacy of endocrine and chemotherapy regimens in patients with hormone-resistant metastatic breast cancer (mBC) after progression with CDK4/6 inhibitors are limited; the search for an effective therapy regimen in this clinical situation is an urgent task of clinical oncology.

Aim. Evaluate the efficacy and safety of eribulin therapy in patients with HR+/HER2- mBC after progression with CDK4/6 inhibitors; compare the results of the Russian study and the EMPOWER observational study in the USA.

Materials and methods. The Russian observational study included 54 patients (pts) with HR+/HER2- mBC, who were treated with eribulin after CDK4/6 inhibitors in 24 Russian cancer hospitals. The median age of pts was 56 years; 75.9% of them had recurrent BC, 24.1% – de novo BC stage IV; 51.9% of pts had progression with CDK4/6 inhibitors in the first 6 months of therapy (primary endocrine resistance); 48.1% of patients had progression in the period from 6 to 38 months; 89.1% had visceral site of metastases (liver MTS – 65.5%, lung MTS – 52.8%, brain MTS in 7.5%). Eribulin was used after anthracyclines and taxanes in 94.4% of cases. The efficacy and safety of eribulin therapy in patients with HR+/HER2- mBC after progression with CDK4/6 inhibitors was studied, as well as subgroup analysis according to age, sites of metastasis, and previously treatment options.

Results. Eribulin was prescribed in the standard regimen of 1.4 mg/m^2 on days 1 and 8, the interval between cycles was 21 days, the number cyclys of chemotherapy was 1–44 (median – 8, the mean number of cycles – 10.5). With a median follow-up of 11.5 months (from 3 to 36 months), 30 patients (55.6%) continue therapy with eribulin at present; therapy was cancelled in 24 patients due to progression in 22 cases (40.7%), and due to intolerable toxicity in 2 patients (3.7%). The maximum response to eribulin therapy included partial response (in 11 cases, 24.4%), stable disease (in 30 cases, 66.7%) and progression in 4 patients (8.9%). Median PFS with eribulin therapy was 10.0 months; the 6-month, 1-year, and 2-year PFS were 79.5%, 44.8% and 26.5%, respectively. Eribulin therapy was equally effective in different subgroups (p>0.05) and did not depend on the age of patients, the previously received treatment, the presence of visceral MTS and liver damage. The best response to chemotherapy with eribulin was observed in lung metastases: median PFS 24 months vs 9.1 months, p=0.056. The safety profile was favorable; adverse events were registered in 34.5% of patients, which required dose adjustment in 18.5% of cases. With a median follow-up of 11.5 months, 92.6% of patients remain alive.

Conclusion. Eribulin has demonstrated high efficacy and favorable safety profile in hormone-resistant HER2- mBC in patients with progression when receiving CDK4/6 inhibitors.

Keywords: HR+/HER2- metastatic breast cancer, CDK4/6, combined endocrine therapy with CDK4/6 inhibitors, hormone resistance, eribulin, eribulin chemotherapy efficacy, eribulin chemotherapy safety, visceral metastases, lung metastases

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ОРИГИНАЛЬНАЯ СТАТЬЯ

Анализ эффективности и безопасности терапии эрибулином у больных HR+HER2-негативным метастатическим раком молочной железы, предлеченных ингибиторами CDK4/6 в условиях реальной российской практики

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Аннотация

Актуальность. Данные об эффективности отдельных режимов эндокринотерапии и химиотерапии (ХТ) у больных гормонорезистентным метастатическим раком молочной железы (мРМЖ) после прогрессирования на ингибиторах CDK4/6 (CDK4/6i) лимитированы; поиск эффективного режима терапии в данной клинической ситуации является актуальной задачей клинической онкологии.

Цель. Оценить эффективность и безопасность терапии эрибулином у больных HR+HER2-негативным мРМЖ после прогрессирования на CDK4/6i; сравнить результаты российского исследования и американского наблюдательного исследования EMPOWER.

Материалы и методы. В российское наблюдательное исследование включены 54 больных HR+HER2-негативным мРМЖ, которые получали лечение в 24 онкологических учреждениях (CDK4/6i; после прогрессирования – эрибулином). Медиана возраста больных составила 56 лет; 75,9% пациенток имели рецидивирующий рак, 24,1% – первично-диссеминированный РМЖ; прогрессирование на CDK4/6i в первые 6 мес терапии имели 51,9% больных, в срок от 6 до 38 мес – 48,1%; висцеральные метастазы (МТС) имели 89,1% (МТС в печень – 65,5%, МТС в легкие – 52,8%), МТС в головной мозг – 7,5% больных. Предшествующая эрибулину ХТ включала антрациклины и таксаны – в 94,4% случаев. Оценена эффективность и безопасность терапии эрибулином у больных HR+HER2-негативным мРМЖ после прогрессирования на CDK4/6i, в том числе и в различным подгруппах, включая возраст, сайты метастазирования, полученное ранее лечение.

Результаты. Эрибулин назначался в стандартном режиме 1,4 мг/м^2 в 1 и 8-й дни, интервал между курсами – 21 день, число проведенных курсов ХТ рибулином составило от 1 до 44, медиана – 8, среднее число – 10,5. При медиане наблюдения за больными 11,5 мес (от 3 до 36 мес) 30 (55,6%) пациенток продолжают терапию эрибулином в настоящее время, у 24 больных терапия отменена, причем в 22 (40,7%) случаях вследствие прогрессирования, у 2 (3,7%) – из-за непереносимой токсичности. Максимальный ответ на терапию эрибулином включал частичный ответ (в 11 случаях, 24,4%), стабилизацию заболевания (в 30 случаях, 66,7%) и прогрессирование – у 4 (8,9%) больных. Медиана выживаемости без прогрессирования (ВБП) на терапии эрибулином составила 10,0 мес; 6-месячная, 1-годичная и 2-летняя ВБП составила соответственно 79,5, 44,8 и 26,5%. Терапия эрибулином была равноэффективна в различных подгруппах (p>0,05) и не зависела от возраста больных, полученного ранее лечения, наличия висцеральных МТС и поражения печени. Лучший ответ на ХТ рибулином отмечен при МТС в легкие: медиана ВБП 24 мес vs 9,1 мес; p=0,056. Профиль безопасности был благоприятным; нежелательные явления отмечены у 34,5% больных, что потребовало коррекции дозы в 18,5% случаев. При медиане наблюдения 11,5 мес 92,6% больных остаются живы.

Заключение. Эрибулин продемонстрировал высокую эффективность и благоприятный профиль безопасности при гормонорезистентном HER2-негативном мРМЖ, у больных с прогрессированием на CDK4/6i.

Ключевые слова: HR+HER2-негативный мРМЖ, CDK4/6, комбинированная эндокринотерапия с ингибиторами CDK4/6, гормонорезистентность, эрибулин, эффективность химиотерапии эрибулином, безопасность химиотерапии эрибулином, висцеральные метастазы, метастазы в легкие

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Breast cancer (BC) is the most common female oncopathology all over the world; a steady increase in morbidity and consistently high mortality rates induce a constant search for new effective regimens for the treatment of this disease. Despite the BC screening and modern treatment strategy about 25–30% of patients with early stages have a further recurrent of the disease; besides, the proportion of the BC de novo stage IV remains very high, both in the world (5–10%) and in the Russian population of women (7.5%) [1–3].

The dominant variant of the disease both in early and advanced stages of BC is the luminal (HR+) HER2-negative tumor subtype, for which multilinear change of endocrine therapy (ET) regimens is a preferred treatment strategy [3–6]. Recent studies show that ET and chemotherapy are equally efficient as initiating treatment for HR+/HER2- metastatic breast cancer (mBC), both in terms of progression-free survival (PFS) and overall survival (OS), but at the same time, ET has a more favorable safety profile compared with cytostatic regimens [7]. The emergence

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of the class of CDK4/6 inhibitors (CDK4/6i) has led to the determination of the preferred regimens for the first and second line of therapy; the combined ET with CDK4/6i (palbociclib, ribociclib, and abemaciclib) has proven its significant advantage in increasing PFS, OS, disease control, and improvement of the quality of life in patients with HR+/HER2- mBC [8–11]. However, every fifth patient showed disease progression in the first year of combined ET despite the high efficacy of CDK4/6i, and the selection of the further treatment strategy (continuation of ET and which exactly) or the start of chemotherapy (selection of cytostatic agents) becomes a highly challenging task in clinical oncology [12–16].

Among the chemotherapy drugs that are effective in HER2-negative mBC, eribulin stands out, while it does not have cross-resistance with other cytostatic agents and effectively works after progression with anthracyclines and taxanes [17–19]. The efficacy of eribulin in the later lines of treatment for BC allowed suggesting that it might be the therapeutic potential in HR+/HER2-negative mBC pretreated with CDK4/6i.

Aim – assessment of the efficacy and safety of eribulin therapy in patients with HR+/HER2- mBC pretreated with CDK4/6i in real Russian practice.

Materials and methods

The article presents the results of the combined Russian experience in assessing the efficacy and safety of chemotherapy with eribulin in 54 women with HR+/HER2- mBC pretreated with CDK4/6i; the study is observational and includes data on patients from 24 Cancer Hospitals of the Russian Federation. The age of the patients varied from 29 to 79 years (median – 56 years); the diagnosis of HR+/HER2-negative BC was verified (based on biopsy of the primary tumor ± distant metastases) in all cases; 75.9% of patients had recurrent cancer, 24.1% had de novo BC stage IV. All patients with mBC received combined ET with CDK4/6i (palbociclib – 75.9%, ribociclib – 22.2%, both CDK4/6i – 1.9%), and aromatase inhibitors (51.9%) or fulvestrant (48.1%) were used as endocrine partners. Early lines with CDK4/6i prescription prevailed: the first line was in 50% of pts, the second line was in 35.2%, the third and subsequent lines were in only 14.8% of pts. Duration of response to CDK4/6i therapy ranged from 2 to 38 months (mean response was 9.1 months); progression on combined ET occurred in 51.9% of patients during the first 6 months of therapy (primary endocrine resistance), and in 48.1% of cases it developed within 6 to 38 months after starting therapy with CDK4/6i. Chemotherapy preceding eribulin (including early stages of BC) included anthracyclines and taxanes in 94.4% pts, in 5.6% of cases – taxanes only. The clinical characteristics of the patients and the treatment received are presented in Table 1.

At the time of the start of chemotherapy with eribulin, visceral metastases were detected in the majority of cases (49/54; 89.1%), moreover, 36 patients (65.5%) had liver metastases, 28 (52.8%) had lung MTS, and 4 patients (7.5%) had brain damage. Bone MTS were diagnosed in 42 patients (79.2%), and MTS in the skin and soft tissues was registered in 10 patients (18.9%); Fig. 1. Among the rare sites of metastasis, tumor lesion of the pericardium in 2 patients, and MTS in the spleen, adrenal gland and intestinal wall in 1 case each should be noted. The majority of patients (73.1%) were diagnosed with lesions of three sites or more.

The patients received eribulin after CDK4/6i according to the indications registered in Russia: as the second and subsequent lines of chemotherapy for metastatic BC after anthracyclines and taxanes, including chemotherapy for the early stages. The efficacy and safety of eribulin therapy in patients with HR+/HER2- mBC after the progression with CDK4/6i was studied; statistical analysis was performed by the international statistical program SPSS 20.0, differences were considered significant at $p<0.05$, survival was calculated using the Kaplan–Meier methods.

Results

Efficacy analysis of eribulin therapy

Eribulin was prescribed as monotherapy at a standard dose of 1.4 mg/m^2 on days 1 and 8 as a 5-minute intravenous infusion, with a 21-days interval between cycles. In the case of the development of serious adverse events, the dose reduction was carried out in a 2-steps: the first reduction step – up to 1.1 mg/m^2 (required by 9 patients, 16.7%) on days 1 and 8, the second reduction step – up to a dose of 0.7 mg/m^2 on days 1 and 8 (required in 1 case, 1.9%); Table 2.

In the majority of patients (49/54; 90.7%), eribulin was used in the initial lines of HR+/HER2-negative mBC therapy: in the second line – 33 (61.1%) pts, in the third line – 16 (29.6%). In the later lines (fourth and fifth), eribulin was prescribed extremely rarely – only in 7.4 and 1.9% of pts, respectively. The number of

Fig. 1. The main sites of metastasis in patients with HR+/HER2- mBC at the start of eribulin therapy.
Рис. 1. Основные сайты метастазирования у больных HR+HER2- мРМЖ на начало терапии эрибулином.

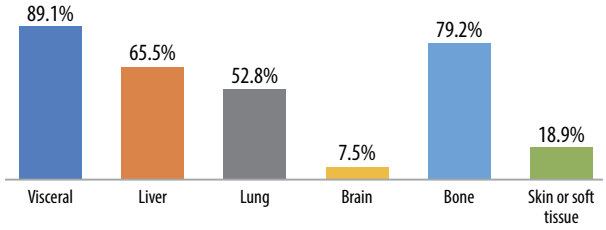

Fig. 2. PFS according to recurrent and de novo stage IV mBC (p=0.389).
Рис. 2. ВБП у больных рецидивирующим и de novo мРМЖ IV стадии (p=0,389).

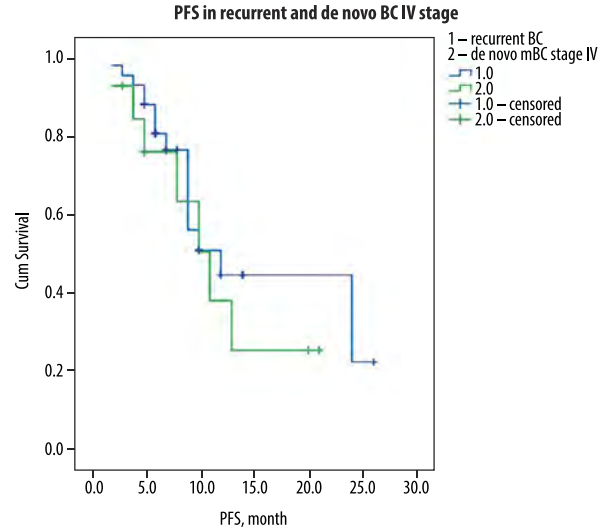

Fig. 3. PFS according to line of eribulin chemotherapy (p=0.567).
Рис. 3. ВБП в зависимости от линии ХТ эрибулином (p=0,567).

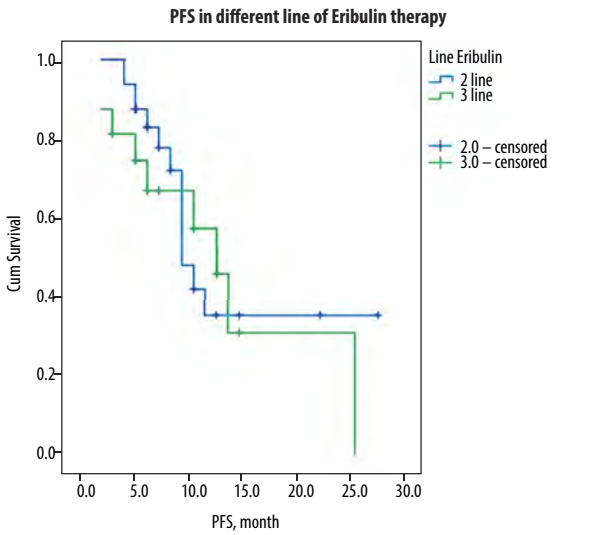

Table 1. Clinical characteristics of patients and the therapy prior to eribulin
Таблица 1. Клиническая характеристика пациенток и предшествующей эрибулину терапии

Clinical Characteristics	Number of Patients, N	% of Patients
Age of patients		
Median (range)	56 (27–79 y.o.)	
Under 40 y.o.	5	9.3
40–50 y.o.	12	22.2
50–60 y.o.	22	40.7
Over 60 y.o.	15	27.8
BC stage		
Recurrent	41	75.9
De novo stage IV	13	24.1
BC stage at the time of primary treatment		
I	9	16.7
IIA	8	14.8
IIB	13	24.1
IIIA	2	3.7
IIIB	15	27.8
IIIC	7	13.0
Histological type of BC		
Invasive ductal	29	53.7
Invasive lobular	6	11.1
Other	19	35.2
Prior therapy with CDK4/6i		
Palbociclib	41	75.9
Ribociclib	12	22.2
Both CDK4/6i	1	1.9
Endocrine partner to CDK4/6i		
Aromatase inhibitors	28	51.9
Fulvestrant	26	48.1
CDK4/6i prescription line		
First	27	50.0
Second	19	35.2
≥Third	8	14.8
Duration of response to CDK4/6i therapy		
Mean response time (range)	9.1 months (2–38)	
Progression in the first 6 months	28	51.9
Progression from 6 to 38 months	26	48.1
Chemotherapy (including early stages of BC)		
Anthracyclines + taxanes	51	94.4
Taxanes only	3	5.6

chemotherapy cycles with eribulin ranged from 1 to 44, the median was 8, and the mean was 10.5 cycles.

With a median follow-up of 11.5 months (from 3 to 36 months), 30 patients (55.6%) continue therapy with eribulin; therapy was cancelled in 24 pts, due to progression in 22 cases (40.7%), and due to intolerable toxicity in 2 patients (3.7%).

The maximum response to eribulin therapy (evaluated in 45 patients) included partial response (in 11 cases, 24.4%), stable of disease (in 30 cases, 66.7%) and progression in 4 pts (8.9%); Table 2. The effectiveness of treatment was not carried out in 9 pts due to a short follow-up period (from 1 to 5 months from the start of treatment). Data on eribulin therapy and its results are presented in Table 2.

Patient survival was assessed with a median follow-up of 11.5 months. Median PFS with eribulin therapy was 10.0 months; 3-months, 6-month, 1-year, and 2-year PFS were 94.4%, 79.5%, 44.8% and 26.5%, respectively. It should be noted that the efficacy of eribulin therapy did not depend on such clinical factors as the age of the patients, p=0.305; previously obtained CDK4/6i (palbociclib/ribociclib), p=0.642; endocrine partner to CDK4/6i (aromatase inhibitors/fulvestrant), p=0.804; the line of prescription of CDK4/6i (p=0.593). Besides, PFS values were high and identical in patients with recurrent and de novo stage IV mBC (p=0.389); Fig. 2, when using eribulin in the second and third lines of chemotherapy (p=0.567); Fig. 3.

Eribulin therapy was equally effective at different sites of metastasis; thus, the median PFS with liver metastases or in their absence was 10 vs 11.8 months, p=0.663 (Fig. 4); with bone metastases/in their absence – 11 vs 9.0 months, p=0.726 (Fig. 5); with skin and soft tissue metastases/in their absence – 9 vs 11 months, p=0.476 (Fig. 6).

The best response to eribulin therapy were observed in patients with lung lesions: the presence of lung MTS was associated with a high sensitivity to eribulin and the best values of the median PFS and these differences are close to statistically significant (24 vs 9.1 months, p=0.056); Fig. 7.

With a median follow-up of 11.5 months, 4 out of 54 patients (92.6%) died from BC progression, 50 out of 54 patients (92.6%) remain alive and continue treatment for mBC.

Safety analysis of eribulin therapy

The safety profile of eribulin therapy was favorable; adverse events associated with eribulin therapy were observed in 19 out of 54 patients (34.5%). Among adverse events of all grades, neutropenia prevailed in 14/54 pts, 25.9%, with G1 in 5.5%, G2 in 11.1%, G3 in 9.3%, while febrile neutropenia was noted in only

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Table 2. Eribulin chemotherapy in patients with CDK4/6i-pretreated HR+/HER2- mBC: main indicators and efficacy assessment
Таблица 2. ХТ эрибулином у больных CDK4/6i-предлеченным HR+HER2- мРМЖ: основные показатели и оценка эффективности

Key Characteristics	Number of Patients, N	% of Patients
Number of cycles of eribulin		
Range	1–44	
Median	8	
Mean number	10.5	
Eribulin chemotherapy line		
Second	33	61.1
Third	16	29.6
Fourth	4	7.4
Fifth	1	1.9
Eribulin dose reduction		
No	45	83.3
Up to 1.1 mg/m^2	9	16.7
Up to 0.7 mg/m^2	1	1.9
Therapy status with a median follow-up of 11.5 months		
Therapy continues	30	55.6
Therapy was discontinued due to progression	22	40.7
Therapy was discontinued due to toxicity	2	3.7
Maximum response to eribulin therapy		
Partial response	11	24.4
Stabilization	30	66.7
Progression	4	8.9

1 case (1.9%). Polyneuropathy was observed in 6 of 54 pts, 11.1%, with G1 in 5.5%, G2 in 3.7%, G3 in 1.8% of cases. Anemia and asthenia were noted in 9.3% of patients, G1 in all cases; alopecia (G1 only) developed in 2/54 patients (3.7%). It should be noted that the development of adverse events did not affect the efficacy of eribulin therapy, p=0.648 (Fig. 8).

The development of adverse events required dose reduction in 10 patients; in 9 out of 54 pts, 16.7% – up to a dose of 1.1 mg/m^2, and a dose reduction to 0.7 mg/m^2 was required in 1 patient (1.9%) only. It is important that the reduction of the eribulin dose did not affect the effectiveness of therapy; the median PFS were similar in patients with the full and reduced doses of the drug (p=0.612); Fig. 9.

Discussion

The current priorities in the treatment of hormone-sensitive HER2- BC are obvious: due to the high antitumor efficacy, proven survival benefit and high quality of life, oncological communities recommend CDK4/6i as first and second lines of therapy for this type of disease. Despite this, about 20% of patients have the progression of the disease already in the first year after starting CDK4/6i therapy [11–16]. The choice of a further treatment strategy after CDK4/6i becomes an urgent and difficult task due to the absent of convincing data on the benefit any tipe of therapy in this situation. When three lines of endocrine therapy are ineffective or when symptoms of a visceral crisis appear, the issue of prescribing chemotherapy becomes obvious for all patients with HR+/HER2- mBC [4–6].

Among the cytostatic agents that have proven efficacy as late lines of therapy, eribulin stands out, while it combines a high antitumor activity and a favorable safety profile. The uniqueness of this drug is caused not only by the absence of cross-resistance to other cytostatic agents and the high efficiency of eribulin after anthracyclines and taxanes but also by the presence of therapeutic potential for various biological subtypes including HR+/HER2- mBC [17–21].

The results of our observational study showes the high efficacy of eribulin in Russian practice in patients after progression on CDK4/6i therapy, which coincides with the data of the large US observational study, EMPOWER, in which 395 patients with HR+/HER2- mBC received combined ET with CDK4/6i and after progression – chemotherapy with eribulin [22]. In the group of patients who received eribulin according to the indications registered in the United States (third-line chemotherapy for mBC after anthracyclines and taxanes), there were 135 patients, who had visceral metastases in 92.6% of cases. The authors showed high rates of eribulin efficacy in such a challenging clinical situation: 26.7% had an objective response, and 54.1% of patients had shown clinical efficacy, the median PFS was not achieved, and the 6-month PFS was observed in 70.4% of patients. The safety profile of therapy was favorable and corresponded to previously reported data: the rate of neutropenia was low in 23% (febrile neutropenia in only 0.7% of cases), peripheral polyneuropathy was registered in 11.1%, and diarrhea in 12.6% of patients. It should be noted that the efficacy of eribulin in the EMPOWER study was assessed only for 64.4% of patients who received this treatment [22].

According to the combined Russian analysis, the population of Russian patients receiving eribulin after CDK4/6i was also characterized by the presence of unfavorable clinical factors: recurrent BC – 75.9%, progression during the first 6 months of therapy with CDK4/6i – 51.9%, visceral MTS – 89.1% (MTS in the liver – 65.5%, MTS in the lungs – 52.8%), MTS in the brain – 7.5%. Despite this, the prescription of eribulin as an early line of chemotherapy (in the second line – 61.1%, in the third line – 29.6%), careful monitoring of toxicity and competent dose reduction made it possible to achieve high rates of treatment efficacy in Russian women (partial response – 24.4%, stable of BC – 66.7%). Patient survival was assessed with a median follow-up of 11.5 months; median PFS was 10.0 months; 3-month, 6-month, 1-year, and 2-year PFS were 94.4%, 79.5%, 44.8% and 26.5%, respectively. It should be noted that the efficacy of eribulin therapy in Russian women did not depend on the age of the patients, previous treatment, and most of the metastatic sites. However, the maximum efficacy of eribulin therapy was observed in patients with lung metastases: in this subgroup the median PFS reached 24 months (without lung MTS – 9.1 months, p=0.056); the search for factors explaining such high therapeutic potential in lung metastases seems to be a very promising task for practical oncology.

The safety profile of eribulin therapy in Russian patients receiving eribulin after CDK4/6i was favorable, which is consistent with the results of the randomized trials and the data from the EMPOWER study analysis. Adverse events associated with eribulin therapy were observed in 34.5%, in most cases – of grade 1 and 2; dose reduction was required in 18.5% of cases. However, the development of adverse events and the dose reduction did not affect the efficacy of eribulin therapy in Russian patients.

Fig. 4. PFS according to liver metastases (p=0.663).
Рис. 4. ВБП в зависимости от наличия/отсутствия МТС в печень (p=0,663).

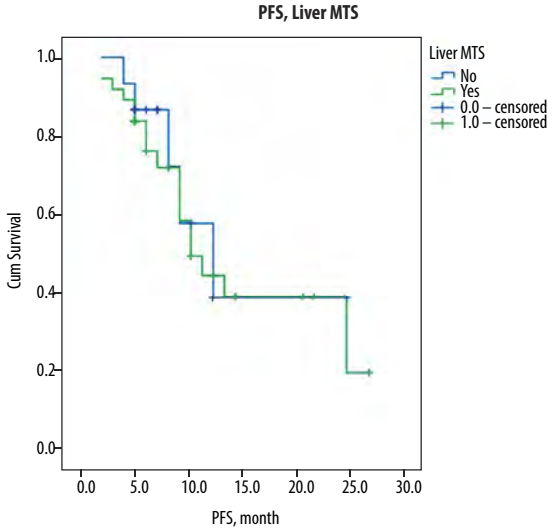


Fig. 5. PFS according to bone metastases (p=0.726).
Рис. 5. ВБП в зависимости от наличия/отсутствия костных МТС (p=0,726).

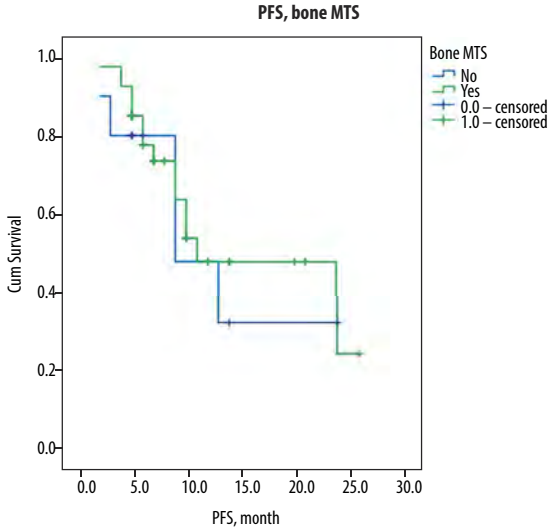


Fig. 6. PFS according to skin and soft tissue metastases (p=0.726).
Рис. 6. ВБП в зависимости от наличия/отсутствия кожных и мягкотканых МТС (p=0,726).

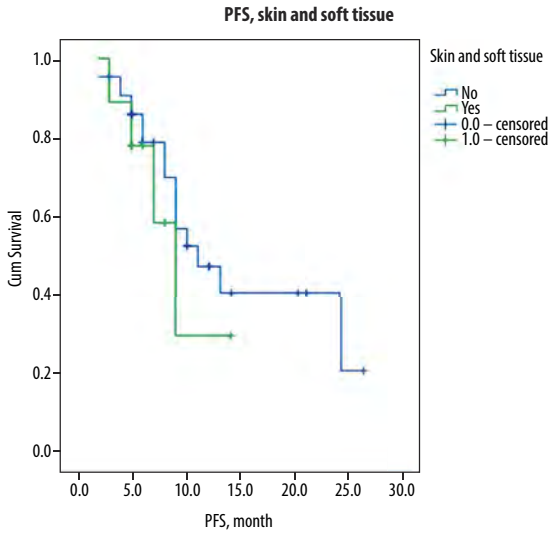


Fig. 7. PFS according to lung metastases (p=0.056).
Рис. 7. ВБП в зависимости от наличия/отсутствия МТС в легкие (p=0,056).

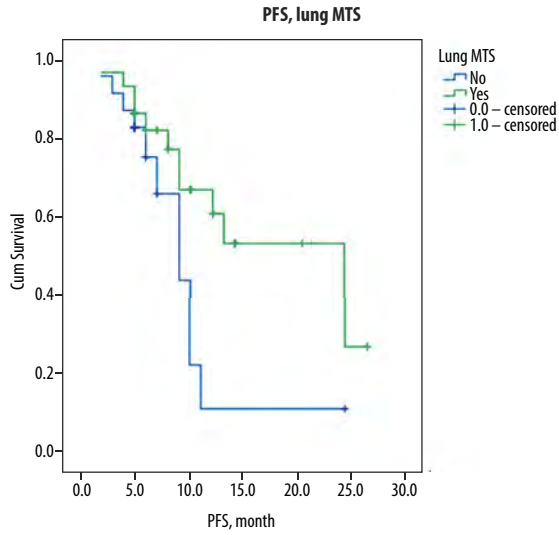


Fig. 8. PFS according to adverse events during eribulin therapy (p=0.648).
Рис. 8. Влияние развития нежелательных явлений при терапии эрибулином на показатели ВБП (p=0,648).

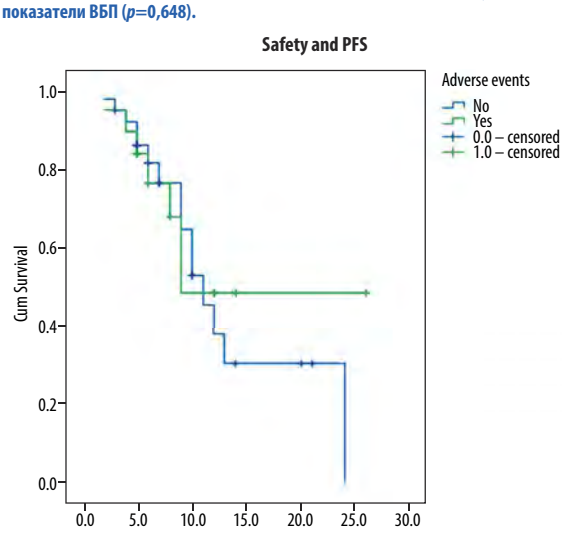
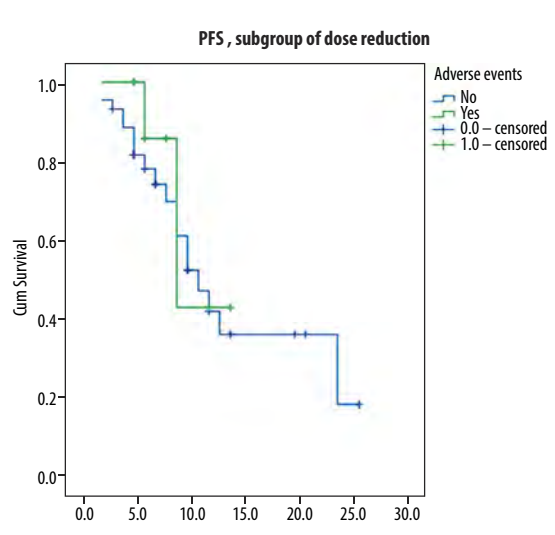


Fig. 9. PFS according to dose reduction of eribulin (p=0.612).
Рис. 9. Влияние редукции дозы эрибулина на показатели ВБП (p=0,612).



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Conclusion

Thus, the first results of the pooled Russian analysis (as well as the results of the US observational study, EMPOWER) give grounds to hope that eribulin may become a promising therapeutic option in patients with hormone-resistant mBC after progression with CDK4/6i.

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